DESCRIPTION

AMINO ALCOHOL DERIVATIVES, SALTS THEREOF AND IMMUNOSUPPRESIVE AGENTS

TECHNICAL FIELD

The present invention relates to amino alcohol derivatives, salts and hydrates thereof that are suitable for use as immunosuppressive agents.

BACKGROUND ART

(Patent Article 1) International Patent Publication No. WO 9408943

(Patent Article 2) Japanese Patent Laid-Open Publication No. Hei 9-2579602

(Patent Article 3) International Patent Publication No. WO 0206268

(Patent Article 4) Japanese Patent Laid-Open Publication No. Hei 2002-53575

(Patent Article 5) Japanese Patent Laid-Open Publication No. Hei 2002-167382

Immunosuppressive agents are widely used as a treatment for autoimmune diseases such as rheumatoid arthritis, nephritis, osteoarthritis of and systemic lupus erythematosus, chronic inflammatory diseases such as inflammatory bowel

disease, and allergic diseases such as asthma and dermatitis. Progress in medicine has led to the rise in the number of tissue and organ transplantations performed each year. In such a situation of modern medicine, having as much control as possible over the rejection following transplantation is a key to a successful transplantation. Immunosuppressive agents also play a significant role in this aspect.

In organ transplantations, antimetabolites, such as azathioprine and mycophenolate mofetil, calcineurin inhibitors, such as cyclosporin A and tacrolimus, and corticosteroid, such as prednisolone are typically used. However, some of these drugs are not effective enough while others require continuous monitoring of the blood drug level to avoid renal failure and other serious side effects. Thus, none of conventional immunosuppressive agents are satisfactory in view of efficacy and potential side effects.

Multiple drug combined-therapy, in which different immunosuppressive drugs with different mechanisms of action are used, is becoming increasingly common for the purposes of alleviating the side effects of the drugs and achieving sufficient immunosuppressive effects. Also, development of new types of immunosuppressive agents that have completely different mechanisms of action is sought.

In an effort to respond to such demands, the present inventors conducted a search for new types of

immunosuppressive agents with main interest in 2-amino-1-ethanol derivatives.

While the use of 2-amino-1,3-propanediol derivatives as immunosuppressive agents has been described in Patent Articles No.1 and No. 2, it has not been previously known that 2-amino-1-ethanol derivatives bearing a diaryl sulfide group or a diaryl ether group, the subject compounds of the present invention, exhibit significant immunosuppressive effects. Although Patent Articles No. 3, No. 4 and No. 5 disclose amino alcohol derivatives that act as immunosuppressive agents, these compounds have different structures from the compounds of the present invention.

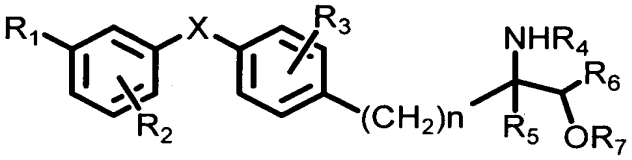
DISCLOSURE OF THE INVENTION

Accordingly, it is an objective of the present invention to provide an amino alcohol derivative that has significant immunosuppressive effects but causes less side effects.

In the course of studies on immunosuppressive agents that act by different mechanism of action than antimetabolites and calcineurin inhibitors, the present inventors discovered that novel diaryl sulfide- or diaryl ether-containing amino alcohol derivatives that have a different structure from known immunosuppressors exhibit strong immunosuppressive effects. Specifically, the compounds each include, at the para-position of one of the two aryl groups, a carbon chain with an amino

alcohol group and also include a particular substituent at the meta-position of the other of the aryl groups. This discovery led the present inventors to devise the present invention.

The present invention thus is an immunosuppressive agent containing as an active ingredient at least one of an amino alcohol derivative, and an optical isomer, a pharmaceutically acceptable salt and a hydrate thereof, the amino alcohol derivative represented by the following general formula (1):



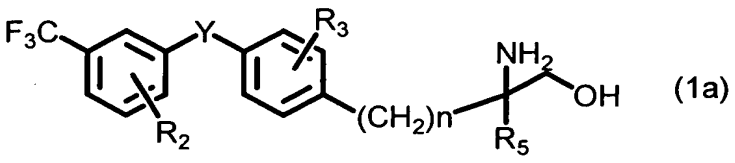
(1)

[wherein R_1 is a halogen atom, a trihalomethyl group, a lower alkyl group having 1 to 4 carbon atoms, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a substituted or unsubstituted phenoxy group, a substituted or unsubstituted aralkyloxy group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, or a lower alkylsulfonyl group having 1 to 4 carbon atoms; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkyl group having 1 to 4 carbon atoms, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, or a aralkyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a benzyloxy group, a lower alkyl group having 1 to 4 carbon atoms, or a lower alkoxythio group having 1 to 4

carbon atoms; R_4 is a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, a phenyl group, a substituted or unsubstituted benzyl group, a lower aliphatic acyl group having 1 to 5 carbon atoms, or a substituted or unsubstituted benzoyl group; R_5 is a hydrogen atom, a monohalogenated methyl group, a lower alkyl group having 1 to 4 carbon atoms, a lower alkoxymethyl group having 1 to 4 carbon atoms, a lower alkylthiomethyl group having 1 to 4 carbon atoms, a hydroxyethyl group, a hydroxypropyl group, a phenyl group, an aralkyl group, a lower alkenyl group having 2 to 4 carbon atoms, or a lower alkynyl group having 2 to 4 carbon atoms; R_6 and R_7 are each independently a hydrogen atom, or a lower alkyl group having 1 to 4 carbon atoms; and X is O, S, SO, or SO_2; and n is an integer from 1 to 4].

BEST MODE FOR CARRYING OUT THE INVENTION

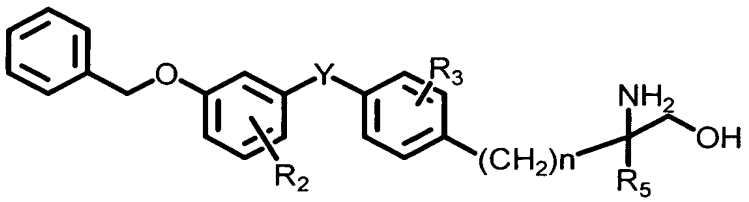
More specifically, the present invention concerns an immunosuppressive agent containing as an active ingredient at least one of an amino alcohol derivative represented by the following general formulae (1a):



(1a)

[wherein Y represents O or S, and R_2, R_3, R_5 and n are as described above], an optical isomer, and a pharmaceutically

acceptable salt thereof, and an amino alcohol derivative represented by the following general formulae (1b):



[wherein Y represents O or S, and R_2, R_3, R_5 and n are as described above], an optical isomer, a pharmaceutically acceptable salt and a hydrate thereof.

The compounds of the general formulae (1), (1a), and (1b) of the present invention are each a novel compound.

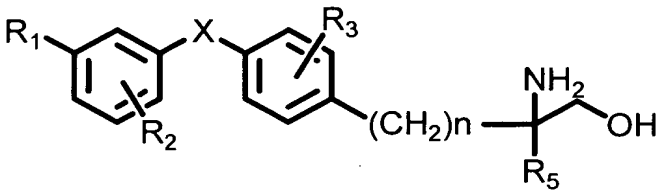
Examples of the pharmaceutically acceptable salts of the compound of the general formula (1) in accordance with the present invention include acid- salts, such as hydrochloride, hydrobromide, acetate, trifluoroacetate, methanesulfonate, citrate, and tartrate.

With regard to the general formula (1), the term "halogen atom" encompasses fluorine, chlorine, bromine, and iodine atoms. The term "trihalomethyl group" encompasses trifluoromethyl and trichloromethyl. The term "lower alkyl" as used in the phrases "lower alkyl group having 1 to 4 carbon atoms," "lower alkoxy group having 1 to 4 carbon atoms," "lower alkylthio group having 1 to 4 carbon atoms," "lower alkylsulfinyl group having 1 to 4 carbon atoms," and "lower alkylsulfonyl group having 1 to 4 carbon atoms" encompasses straight-chained or branched hydrocarbons having 1 to 4 carbon

atoms, such as methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. The phrases "substituted or unsubstituted phenoxy group," "substituted or unsubstituted aralkyl group," "substituted or unsubstituted benzoyl group," and "substituted or unsubstituted benzyl group" encompass those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine atoms, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, and lower having 1 to 4 carbon atoms. The term "aralkyl group" as in "aralkyl group" or "aralkyloxy group" encompasses benzyl, diphenylmethyl, phenethyl, and phenylpropyl. As used herein, the phrase "lower aliphatic acyl group having 1 to 5 carbons" emcompasses straight-chained or branched lower aliphatic acyl groups having 1 to 5 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, and pivaloyl. The phrase "lower alkenyl group having 2 to 4 carbon atoms" as used herein encompasses hydrocarbons having 2 to 4 carbon atoms and having unsaturated double bonds, such as vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 2-methylallyl, and 3-butenyl. The phrase "lower alkynyl group having 2 to 4 carbon atoms" as used herein encompasses hydrocarbons having 2 to 4 carbon atoms and having unsaturated triple bonds, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

Of the compounds of the general formula (1), those in

which each of R_4, R_6, and R_7 is a hydrogen atom are represented by the following general formula (1c):

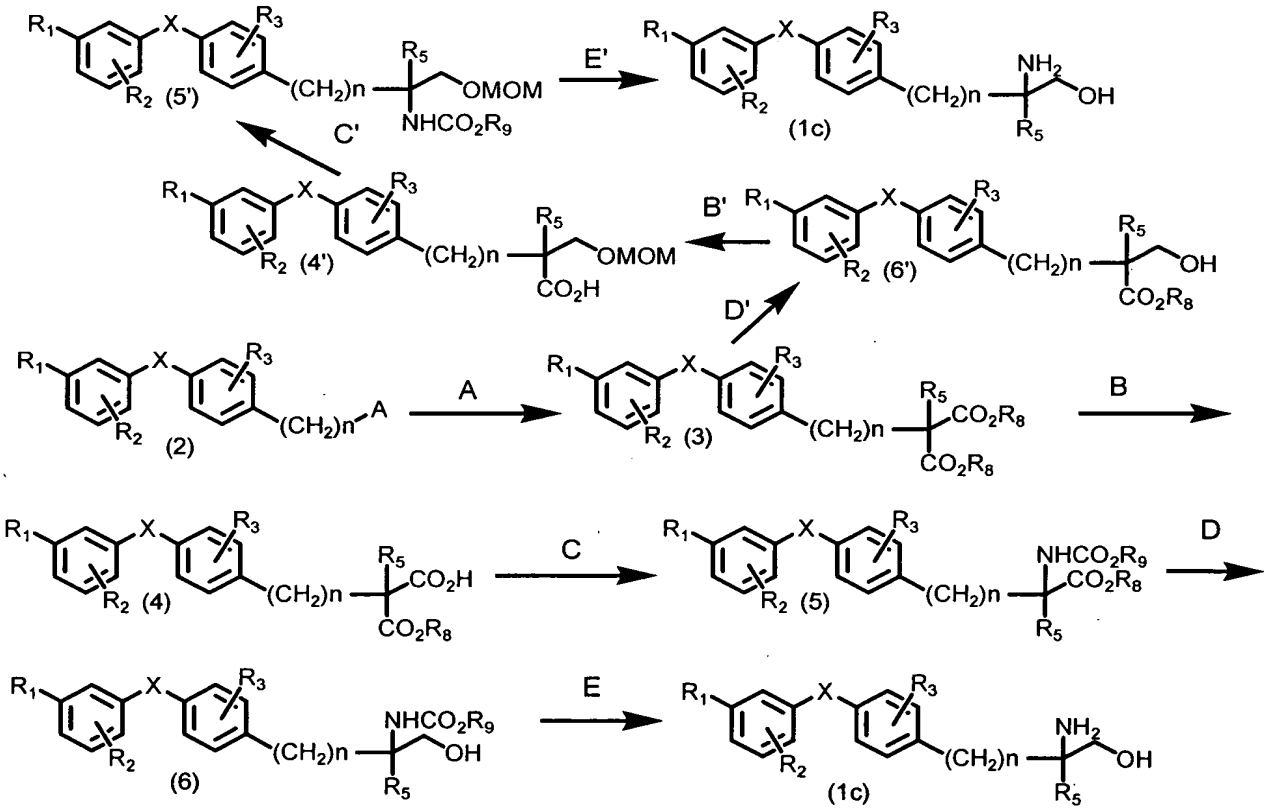


(1c)

[wherein R_1, R_2, R_3, R_5, X, and n are as described above].

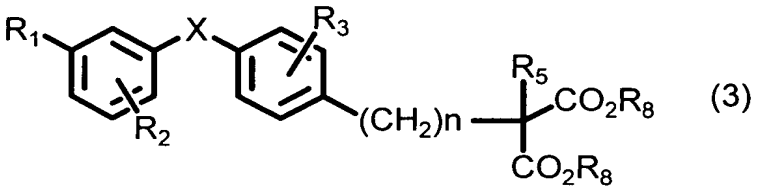
According to the present invention, these compounds can be produced by the following pathway.

Synthetic pathway 1



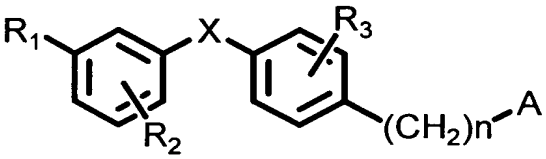
In the synthetic pathway 1, the compound represented by the general formula (3) can be obtained by reacting the compound represented by the general formula (2) with the

compound represented by the general formula (7) in the presence of a base (Step A):



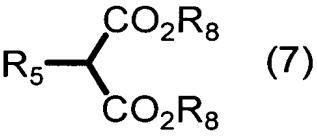
(3)

[where R_8 represents a lower alkyl group having 1 to 4 carbon atoms, and R_1, R_2, R_3, R_5, X, and n are as described above;



(2)

[wherein A represents a chlorine atom, a bromine atom, an iodine atom, or a fluorine atom, and R_1, R_2, R_3, X, and n are as described above]; and



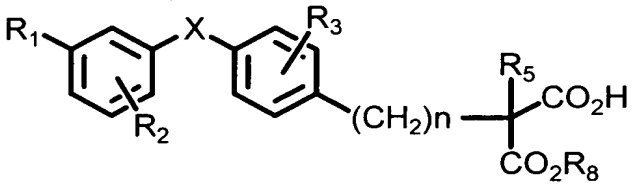
(7)

[wherein R_5 and R_8 are as described above].

This reaction uses a reaction solvent, such as methanol, ethanol, 1,4-dioxane, dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), and tetrahydrofuran (THF), and is carried out at a temperature of 0°C to refluxing temperature, preferably 80°C to 100°C, in the presence of inorganic base, such as sodium hydride, potassium hydride, sodium alkoxide, potassium alkoxide, potassium carbonate, and sodium carbonate.

In the synthetic pathway 1, the compound represented by the general formula (4) can be obtained by hydrolyzing the

compound of the general formula (3) (Step B):

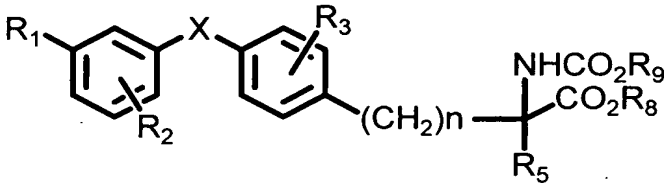


(4)

[wherein R_1, R_2, R_3, R_5, R_8, X, and n are as described above].

This reaction is carried out at a temperature of 0°C to refluxing temperature in the presence of a base, such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide, and in a reaction solvent such as methanol, ethanol, 1,4-dioxane, DMF, or DMSO. Preferably, the reaction is carried out at 50°C in ethanol solvent and in the presence of potassium hydroxide.

In the synthetic pathway 1, the compound represented by the general formula (5) can be obtained by Curtius rearrangement of the compound of the general formula (4) (Step C):



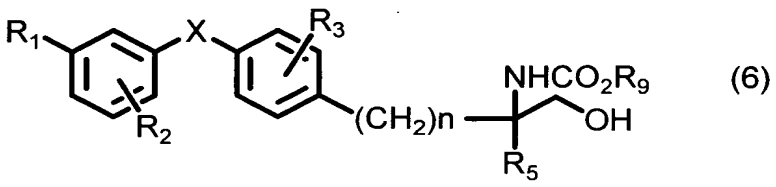
(5)

wherein R_9 represents a lower alkyl group having 1 to 4 carbon atoms, and R_1, R_2, R_3, R_5, R_8, X, and n are as described above.

This reaction can be carried out by a common process to convert a carboxyl group into carbamate. One such process involves ethyl chlorocarbonate and NaN_3. In another process, diphenyl phosphorazidate (DPPA) in benzene or toluene is

stirred in the presence of a base such as triethylamine while the reaction mixture is heated. Subsequently, a lower alcohol, such as methanol, ethanol, propanol, isopropanol, butanol or t-butanol, is added and the mixture is further stirred while being heated. In still another process, a lower alcohol alone is used as the reaction solvent and the reaction mixture is stirred or refluxed while being heated.

In the synthetic pathway 1, the compound represented by the general formula (6) can be obtained by reducing the compound of the general formula (5) (Step D):



(6)

[wherein R_1, R_2, R_3, R_5, R_9, X, and n are as described above].

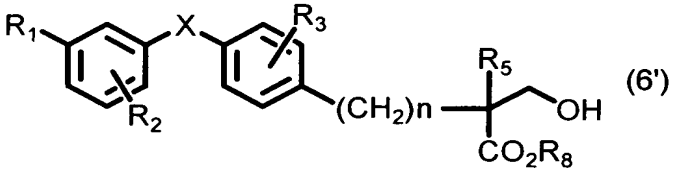
This reaction uses borane (BH_3), an alkylborane derivative, such as 9-borabicyclo[3.3.1]nonane (9-BBN), or a metal hydride complex, such as diisobutyl aluminum hydride ($(iBu)_2AlH$), sodium borohydride ($NaBH_4$), and lithium aluminum hydride ($LiAlH_4$), and preferably uses lithium borohydride ($LiBH_4$). The reaction is carried out at a temperature of 0°C to refluxing temperature, preferably at room temperature, by using THF, 1.4-dioxane, methanol, or ethanol as a reaction solvent.

In the synthetic pathway 1, the compound represented by the general formula (1c) can be obtained by acidolysis or

hydrolysis of the compound of the general formula (6) (Step E).

This reaction is carried out at a temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF as a reaction solvent and is carried out at a temperature of 0°C to refluxing temperature, preferably 80°C to 100°C, in the presence of a base, such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide.

In the synthetic pathway 1, the compound represented by the general formula (6') can be obtained by reducing the compound of the general formula (3) (Step D'):



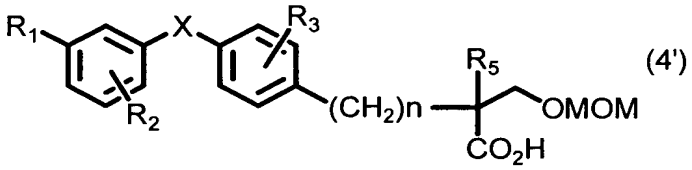
(6')

[wherein R_1, R_2, R_3, R_5, R_8, X, and n are as described above].

This reaction uses an alkylborane derivative, such as BH_3 or 9-BBN, or a metal hydride complex, such as $(iBu)_2AlH$, $NaBH_4$, $LiBH_4$, or $LiAlH_4$, in particular, lithium tributoxy aluminum hydride ($LiAl(t\text{-}BuO)_3$), along with a reaction solvent such as 1,4-dioxane, ethanol, or methanol, in particular, THF. The reaction is carried out at a temperature of 0°C to refluxing

temperature and, preferably, at room temperature.

In the synthetic pathway 1, the compound represented by the general formula (4') can be obtained by protecting the hydroxyl group of the compound of the general formula (6') with methoxymethyl (MOM) group and subsequently hydrolyzing the ester (Step B'):



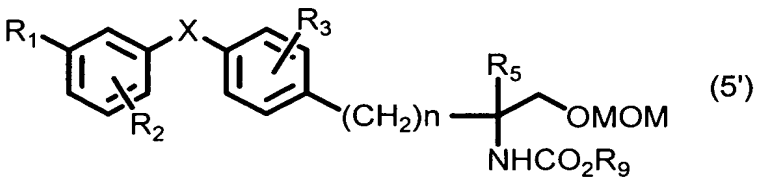
(4')

[wherein MOM represents a methoxymethyl group, and R_1, R_2, R_3, R_5, X, and n are as described above.

This reaction uses a base, such as triethylamine, or pyridine, in particular, diisopropylethylamine, along with an organic solvent, such as THF, 1,4-dioxane, methylene chloride, chloroform, or acetonitrile. The compound of the general formula (6') is first reacted with methoxymethyl chloride or methoxymethyl bromide at 0°C to room temperature to introduce the MOM group. Subsequently, the protected compound is hydrolyzed in a reaction solvent, such as methanol, ethanol, 1,4-dioxane, DMF, or DMSO, at a temperature of 0°C to refluxing temperature and in the presence of a base, such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide.

In the synthetic pathway 1, the compound represented by the general formula (5') can be obtained by Curtius

rearrangement of the compound of the general formula (4') (Step C'):



(5')

[wherein R_1, R_2, R_3, R_5, R_9, MOM, X, and n are as described above].

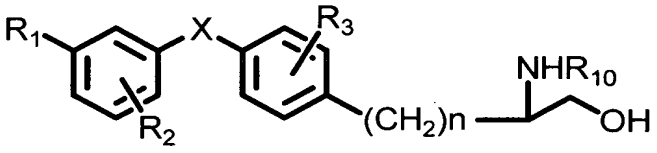
This reaction can be carried out by a common process to convert a carboxyl group into carbamate. One such process involves ethyl chlorocarbonate and NaN_3. In another process, diphenyl phosphorazidate (DPPA) in benzene or toluene is stirred in the presence of a base such as triethylamine while the reaction mixture is heated. Subsequently, a lower alcohol, such as methanol, ethanol, propanol, isopropanol, butanol, or t-butanol, is added and the mixture is further stirred while being heated. In still another process, a lower alcohol alone is used as the reaction solvent and the reaction mixture is stirred or refluxed while being heated.

The compound represented by the general formula (1c) can be obtained by acidolysis or hydrolysis of the compound of the general formula (5') (Step E').

This reaction is carried out at a temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture

with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate. Alternatively, the carbamate group is first deprotected in a reaction solvent, such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF, at a temperature of 0°C to refluxing temperature, preferably 80°C to 100°C, and in the presence of a base, such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide. Subsequently, the MOM group is eliminated by acidolysis.

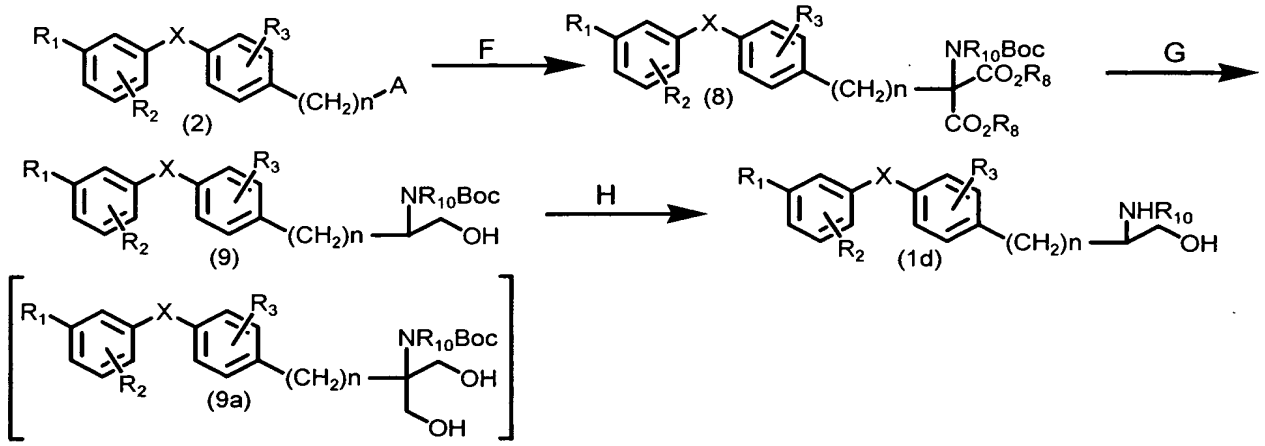
Of the compounds of the general formula (1), those in which R_4 is a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, a phenyl group or a substituted or unsubstituted benzyl group, and R_5, R_6, and R_7 are each a hydrogen atom are represented by the following general formula (1d):



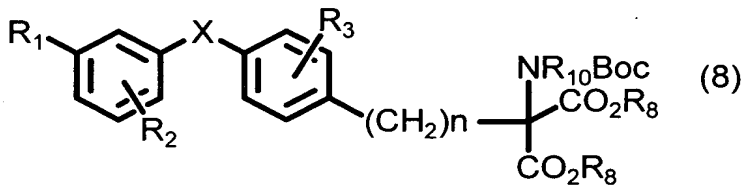
(1d)

[wherein R_{10} is a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, a phenyl group, or a substituted or unsubstituted benzyl group; and R_1, R_2, R_3, X, and n are as described above]. These compounds can be produced by the following pathway:

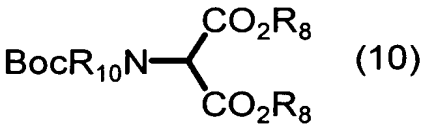
Synthetic pathway 2



In the synthetic pathway 2, the compound represented by the general formula (8) can be obtained by reacting the compound represented by the general formula (2) with the compound represented by the general formula (10) in the presence of a base (Step F):



[wherein Boc represents t-butoxycarbonyl; and R_1, R_2, R_3, R_8, R_{10}, X, and n are as described above]; and

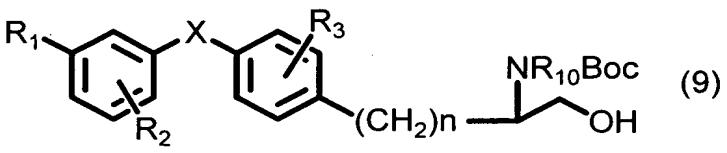


[wherein R_8, R_{10}, and Boc are as described above].

This reaction uses a reaction solvent such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF, and is carried out at a temperature of 0°C to refluxing temperature, preferably 80°C to 100°C, in the presence of an inorganic base, such as sodium

hydride, potassium hydride, sodium alkoxide, potassium alkoxide, potassium carbonate, or sodium carbonate.

In the synthetic pathway 2, the compound represented by the following general formula (9) can be obtained by reducing the compound of the general formula (8) (Step G):



(9)

[wherein R_1, R_2, R_3, R_{10}, X, Boc, and n are as described above].

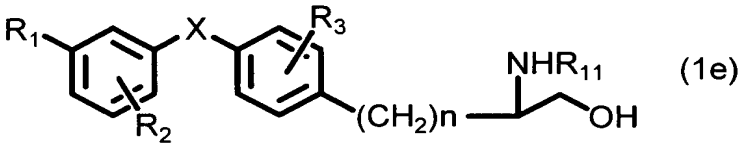
This reaction uses an alkylborane derivative, such as BH_3 or 9-BBN, or a metal hydride complex, such as $(iBu)_2AlH$, $NaBH_4$, and $LiAlH_4$, in particular $LiBH_4$, in a reaction solvent, such as THF, 1,4-dioxane, ethanol, or methanol. The reaction is carried out at a temperature of 0°C to refluxing temperature and, preferably, at room temperature.

In the synthetic pathway 2, the compound represented by the general formula (1d) can be obtained by acidolysis of the compound of the general formula (9) (Step H).

This reaction is carried out at a temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate.

Of the compounds of the general formula (1), those in

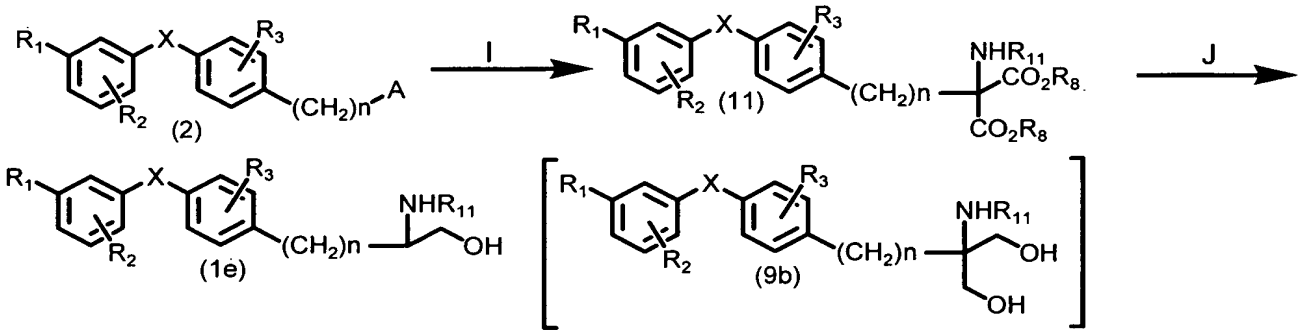
which R_4 is a lower acyl group having 1 to 5 carbon atoms or a substituted or unsubstituted benzoyl group, and R_5, R_6, and R_7 are each a hydrogen atom are represented by the following general formula (1e):



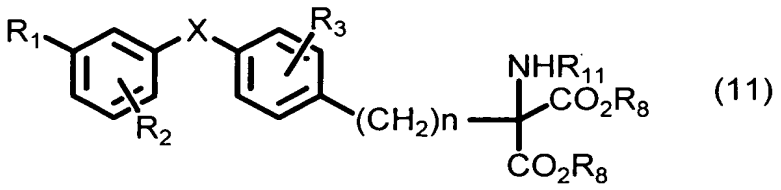
(1e)

[wherein R_{11} is a lower aliphatic acyl group having 1 to 5 carbon atoms or a substituted or unsubstituted benzoyl group; and R_1, R_2, R_3, X, and n are as described above]. These compounds can be produced by the following synthetic pathway 3:

Synthetic pathway 3



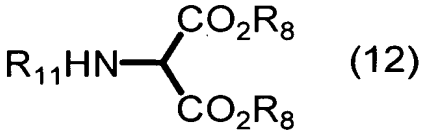
In the synthetic pathway 3, the compound represented by the following general formula (11) can be obtained by reacting the compound represented by the general formula (2) with the compound represented by the general formula (12) in the presence of a base (Step I):



(11)

[wherein R_1, R_2, R_3, R_8, R_{11}, X, and n are as described above];

and



(12)

[wherein R_8 and R_{11} are as described above].

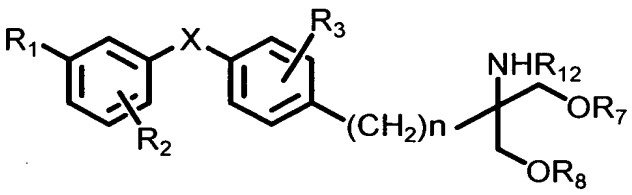
This reaction uses a reaction solvent, such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF, and is carried out at a temperature of 0°C to refluxing temperature, preferably 80°C to 100°C, in the presence of inorganic base, such as sodium hydride, potassium hydride, sodium alkoxide, potassium alkoxide, potassium carbonate, or sodium carbonate.

In the synthetic pathway 3, the compound represented by the general formula (1e) can be obtained by reducing the compound of the general formula (11) (Step J).

This reaction uses an alkylborane derivative, such as BH_3 or 9-BBN, or a metal hydride complex, such as $(iBu)_2AlH$, $NaBH_4$, or $LiAlH_4$, in particular $LiBH_4$, in a reaction solvent, such as THF, 1,4-dioxane, ethanol, or methanol. The reaction is carried out at a temperature of 0°C to refluxing temperature and, preferably, at room temperature.

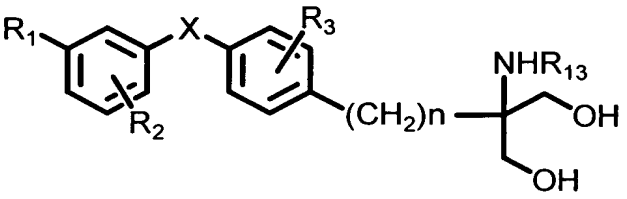
Of the compounds of the general formula (1), those in which R_4 is a hydrogen atom, a lower aliphatic acyl group

having 1 to 5 carbon atoms, or a substituted or unsubstituted benzoyl group, R_5 is a lower alkoxymethyl group having 1 to 4 carbon atoms, and R_6 is a hydrogen atom are represented by the following general formula (1f):



(1f)

[wherein R_{12} is a hydrogen atom, a lower aliphatic acyl group having 1 to 5 carbon atoms, or a substituted or unsubstituted benzoyl group; and R_1, R_2, R_3, R_7, R_8, X, and n are as described above]. These compounds can be obtained by reacting a diol that results from the synthetic pathway 2 or 3 and is represented by the following general formula (9c), with the compound represented by the following general formula (13), and subsequently subjecting the reaction product to acidolysis, if necessary:



(9c)

[wherein R_{13} is a lower aliphatic acyl group having 1 to 5 carbons, a substituted or unsubstituted benzoyl group or Boc; and R_1, R_2, R_3, X, and n are as described above]; and

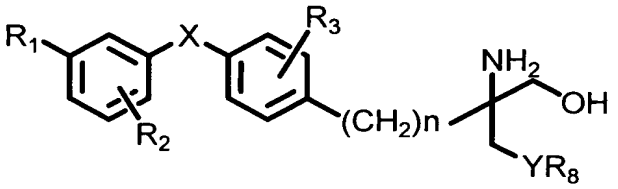
R_8—A (13)

[wherein R_8 and A are as described above].

This reaction may use a reaction solvent such as

methylene chloride, THF, or 1,4-dioxane and is carried out at 0°C to room temperature in the presence of a base, such as triethylamine or pyridine. Preferably, the reaction is carried out at room temperature in acetonitrile and in the presence of silver oxide. When R_{13} in the general formula (9c) is Boc, the acidolysis is carried out at a temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate.

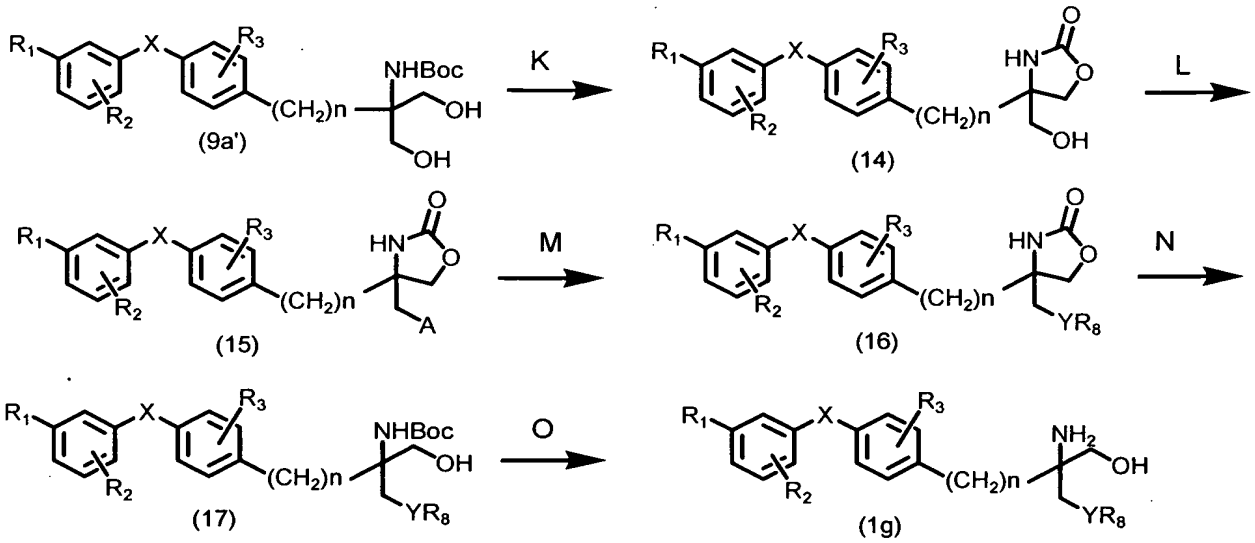
Of the compounds of the general formula (1), those in which R_5 is a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthiomethyl group having 1 to 4 carbon atoms, and R_4, R_6 and R_7 are each a hydrogen atom are represented by the following general formula (1g):



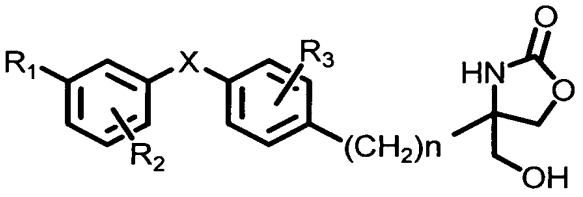
(1g)

[wherein Y represents an oxygen or sulfur atom; and R_1, R_2, R_3, R_8, X, and n are as described above]. These compounds can be obtained by the following synthetic pathway:

Synthetic pathway 4

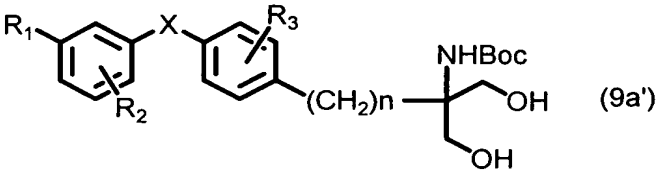


In the synthetic pathway 4, the compound represented by the following general formula (14) can be obtained from the compound represented by the following general formula (9a'), which is the general formula (9a) with R_{10} being a hydrogen atom (Step K):



(14)

[wherein R_1, R_2, R_3, X, and n are as described above]; and



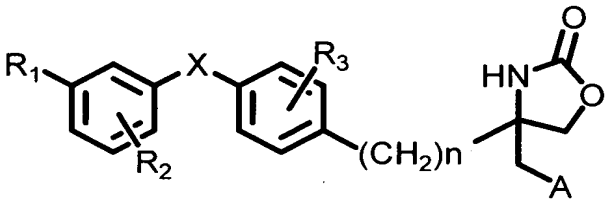
(9a')

[wherein R_1, R_2, R_3, Boc, X, and n are as described above].

This reaction uses a reaction solvent such as THF, 1,4-dioxane, DMF, benzene, or toluene and is carried out at a temperature of 0°C to refluxing temperature, preferably at room

temperature, in the presence of an inorganic base, such as sodium hydride, potassium hydride, sodium alkoxide, or potassium alkoxide. Alternatively, the reaction may be carried out in pyridine solvent while the reaction mixture is refluxed, preferably at 80°C to 100°C.

In the synthetic pathway 4, the compound represented by the following general formula (15) can be obtained by substituting the hydroxyl group of the compound of the general formula (14) with a halogen atom (Step L):



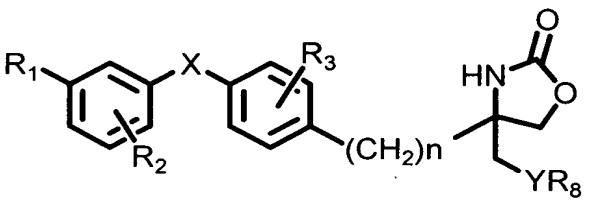
(15)

wherein R_1, R_2, R_3, A, X, and n are as described above.

The reaction uses a reaction solvent such as methylene chloride, THF, or 1,4-dioxane and is carried out at 0°C to room temperature. Specifically, the compound of the general formula (14) is reacted with carbon tetrachloride, carbon tetrabromide, or iodine in the presence of triphenylphosphine or imidazole. Alternatively, the compound of the general formula (14) may be reacted with para-toluene sulfonyl chloride or methanesulfonyl chloride in a solvent such as methylene chloride, chloroform, or benzene in the presence of an organic base such as pyridine or triethylamine to form a corresponding sulfonic acid ester. The reaction is carried out at 0°C to 80°C, preferably at room temperature. Subsequently, the resulting sulfonic acid ester

is reacted with sodium bromide, potassium bromide, sodium iodide, potassium iodide, potassium fluoride, or sodium fluoride. This reaction uses a reaction solvent such as THF, acetonitrile and, preferably, acetone and is carried out at room temperature to refluxing temperature.

In the synthetic pathway 4, the compound represented by the following general formula (16) can be obtained by reacting the compound of the general formula (15) with the compound represented by the following general formula (18) (Step M):



(16)

[wherein R_1, R_2, R_3, R_8, X, Y, and n are as described above], and

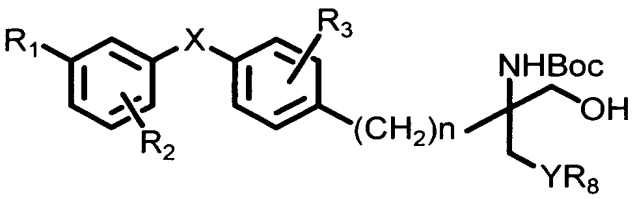
R_8–YH (18)

[wherein R_8 and Y are as described above].

This reaction uses a reaction solvent such as methanol, ethanol, 1,4-dioxane, or DMF and is carried out at 0°C to room temperature in the presence of an organic base, such as triethylamine or pyridine, or an inorganic base, such as sodium hydride, sodium methoxide, sodium ethoxide, sodium butoxide, or potassium butoxide.

In the reaction pathway 4, the compound represented by the following general formula (17) is obtained by introduction of a Boc group to the compound of the general formula (16),

followed by ring-opening of the oxazolidinone ring (Step N):



(17)

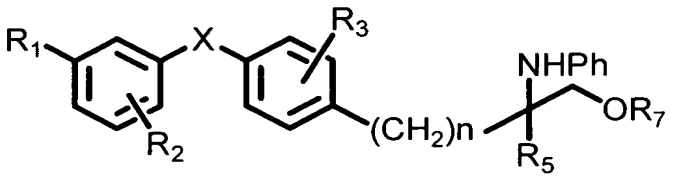
[wherein R_1, R_2, R_3, R_8, X, Y, and n are as described above].

The ring-opening reaction uses a reaction solvent such as THF or 1,4-dioxane, preferably acetonitrile and is carried out under typical Boc-adding conditions. Preferably, the reaction is carried out by first applying Boc_2O at room temperature to 80°C in the presence of dimethylaminopyridien to form a Boc-added form and subsequently opening the oxazolidinone ring at room temperature in methanol solvent in the presence of cesium carbonate.

In the synthetic pathway 4, the compound represented by the general formula (1g) can be obtained by acidolysis of the compound of the general formula (17) (Step O).

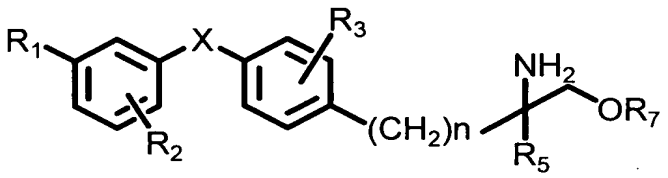
This reaction is carried out at a temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate.

Of the compounds of the general formula (1), those in which R_4 is a phenyl group and R_6 is a hydrogen atom are represented by the following general formula (1h):



(1h)

[wherein R_1, R_2, R_3, R_5, X, and n are as described above]. These compounds can be obtained by reacting the compound represented by the following general formula (1i) with a phenyl bismuth reagent:

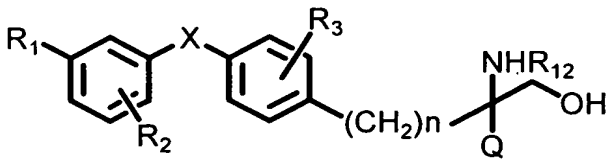


(1i)

[wherein R_1, R_2, R_3, R_5, R_7, X, and n are as described above].

Preferably, this reaction uses methylene chloride as a reaction solvent and is carried out at room temperature by adding $Ph_3Bi(OAc)_2$ and, if necessary, molecular sieves, in the presence of copper acetate.

Of the compounds of the general formula (1), those in which R_4 is a hydrogen atom, a lower aliphatic acyl group having 1 to 5 carbon atoms, or a substituted or unsubstituted benzoyl group, R_5 is a lower alkenyl group having 2 to 4 carbon atoms, and R_6 and R_7 are each a hydrogen atom are represented by the following general formula (1j):



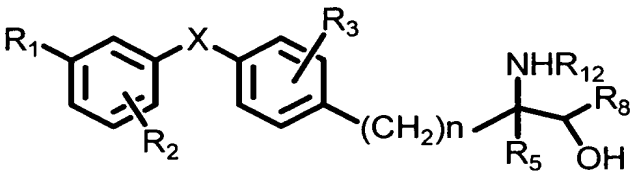
(1j)

[wherein Q is a lower alkenyl group having 2 to 4 carbon atoms, and R_1, R_2, R_3, R_{12}, X, and n are as described above]. These compounds can be obtained by first protecting one of the hydroxyl groups of the compound of the general formula (9c), subsequently oxidizing the remaining hydroxyl group to an aldehyde, forming an alkenyl group by the Wittig reaction, and performing deprotection, if necessary.

Specifically, one of the hydroxyl groups is first protected by a common hydroxyl-protecting group, including an acyl-type protecting group, such as acetyl and benzoyl, a silyl-type protecting group, such as t-butyldimethylsilyl and t-butyldiphenylsilyl, and an alkyl-type protecting group, such as benzyl. DMSO oxidation is then performed to obtain an aldehyde. This is carried out by using an oxidizing agent, including chromium oxide-pyridine complex, such as pyridinium chlorochromate or pyridinium dichromate, a metal oxidizing agent, such as chromium oxide, silver carbonate, or manganese dioxide, or a DMSO activating agent, such as oxalyl chloride, trifuluoroacetic anhydride, acetic anhydride, DCC, or sulfur trioxide-pyridine complex. The aldehyde is then subjected to Wittig reaction. The Wittig reaction uses a reaction solvent such as THF, ether, DMSO, or 1,4-dioxane in conjunction with a phosphonium salt having a lower alkyl group such as methyl, ethyl, propyl isopropy, or butyl and is carried out at -78°C to room temperature in the presence of a base, such as sodium

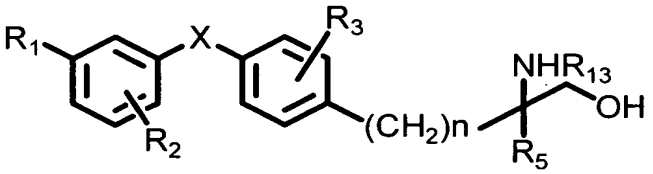
hydride, potassium hydride, sodium butoxide, potassium butoxide, or lithium diisopropylamide. When an acyl-type protecting group is used, the subsequent deprotection of hydroxyl group uses a reaction solvent such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF and is carried out at 0°C to room temperature in the presence of a base, such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide. When a silyl-type protecting group is used, THF, DMF or 1,4-dioxane is used as a solvent and the deprotection reaction is carried out by applying potassium fluoride, cesium fluoride, or tetrabutylammonium fluoride at 0°C to room temperature. For a benzyl protecting group, the deprotection is carried out by a common contact reduction process. For a methoxymethyl protecting group, the deprotection is carried out in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate. When R_{13} in the general formula (9c) is a Boc group, it may be removed by carrying out acidolysis in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate.

Of the compounds of the general formula (1), those in which R_4 is a hydrogen atom, a lower aliphatic acyl group having 1 to 5 carbon atoms, or a substituted or unsubstituted benzyl group, R_6 is a lower alkyl group having 1 to 4 carbon atoms, and R_7 is a hydrogen atom are represented by the following general formula (1k):



(1k)

[wherein R_1, R_2, R_3, R_5, R_8, R_{12}, X, and n are as described above]. These compounds can be obtained by oxidizing the compound represented by the following general formula (11) to an aldehyde, reacting the aldehyde with an organometal reagent, and perfoming deprotection, if necessary:



(1l)

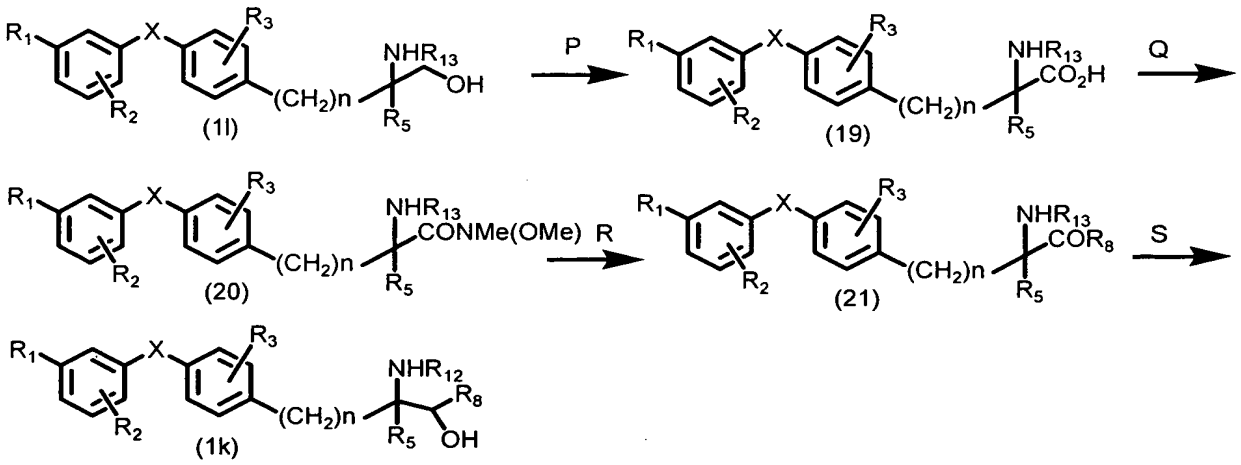
[wherein R_1, R_2, R_3, R_5, R_8, R_{13}, X, and n are as described above].

The oxidation can be carried out by using any methods commonly used for oxidizing an alcohol to an aldehyde. One example is the DMSO oxidation using an oxiding agent, including a chromium oxide-pyridine complex, such as pyridinium chlorochromate or pyridinium dichromate, a metal oxiding agent, such as chromium oxide, silver carbonate and

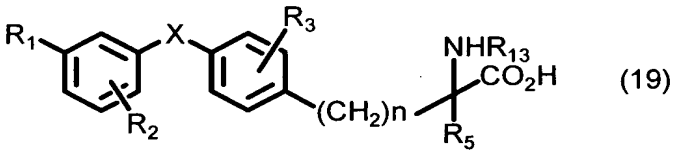
manganese dioxide, or a DMSO activating agent, such as oxalyl chloride, trifuluoroacetic anhydride, acetic anhydride, DCC and sulfur trioxide-pyridine complex. The resulting aldehyde is reacted with a lower alkyl lithium or a lower alkyl Grignard reagent having methyl, ethyl, propyl, isopropyl, or butyl. The reaction is carried out at 0°C to room temperature in a reaction solvent such as THF, ether, or 1,4-dioxane. When R_{13} is a Boc group, the deprotection is carried out at 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate. When R_{13} is a lower aliphatic acyl group or a substituted or unsubstituted benzoyl group that requires deprotection, the deprotection is carried out at 0°C to refluxing temperature, preferably at 80°C to 100°C, in a reaction solvent such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide.

The compound represented by the general formula (1k) can also be obtained by the following alternative synthetic pathway:

Synthetic pathway 5



In the synthetic pathway 5, the compound represented by the following general formula (19) can be obtained by oxidation of the compound of the general formula (1l) (Step P):



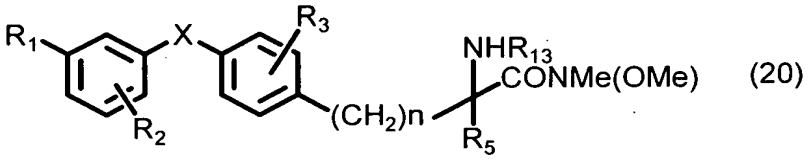
(19)

[wherein R_1, R_2, R_3, R_5, R_{13}, X, and n are as described above].

This reaction uses an oxidizing agent, such as potassium permanganate, lead tetraacetate, luthenium tetraoxide, or, preferably, chromium oxide-pyridine complex, such as pyridinium chlorochromate or pyridinium dichromate, and is carried out at 0°C to room temperature in a reaction solvent, such as acetone, DMF, methylene chloride, chloroform, ethyl acetate, or acetic acid.

In the synthetic pathway 5, the compound represented by the following general formula (20) can be obtained by

condensation of N,O-dimethylhydroxylamine with the compound of the general formula (19) (Step Q):

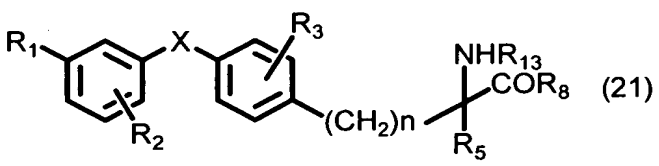


(20)

[wherein R_1, R_2, R_3, R_5, R_{13}, X, and n are as described above].

This reaction can be carried out by using acid anhydride mixture method or active ester method, each commonly used in forming peptide bonds, and preferably involves a condensation agent. Specifically, the reaction uses a reaction solvent such as THF, DMSO, DMF, or methylene chloride and is carried out at 0°C to room temperature in the presence of an organic base such as triethylamine or pyridine, along with a condensation agent such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIPC), DPPA, diethylphosphonylcyanide (DEPC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC), with 4-dimethylaminopyridine (DMAP) optionally added as a catalyst.

In the synthetic pathway 5, the compound represented by the following general formula (21) can be obtained by reacting the compound of the general formula (20) with the compound represented by the following general formula (22) (Step R):



(21)

[wherein R_1, R_2, R_3, R_5, R_8, R_{13}, X, and n are as described above]; and

R_8—M (22)

[wherein M represents Li, MgCl, MgBr, or MgI and R_8 is as described above].

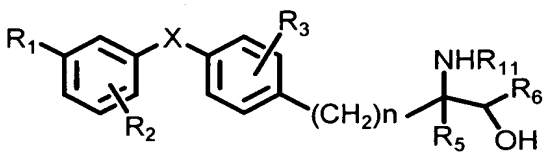
The reaction uses a organic solvent such as ether, 1,4-dioxane, or THF and is carried out at -78°C to room temperature.

In the synthetic pathway 5, the compound represented by the general formula (1k) can be obtained by reducing the compound of the general formula (21), followed, if necessary, by deprotection.

This reaction uses an alkylborane derivative, such as BH_3 or 9-BBN, or a metal hydride complex, such as $(iBu)_2AlH$, $NaBH_4$, or $LiAlH_4$, in particular, $LiBH_4$, in a reaction solvent such as THF, 1,4-dioxane, ethanol, or methanol. The reaction is carried out at a temperature of 0°C to refluxing temperature and, preferably, at room temperature. When R_{13} is a Boc group, the deprotection is carried out at 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate. When R_{13} is a lower aliphatic acyl group or a substituted or unsubstituted benzoyl group that requires deprotection, the deprotection is carried out at 0°C to refluxing temperature,

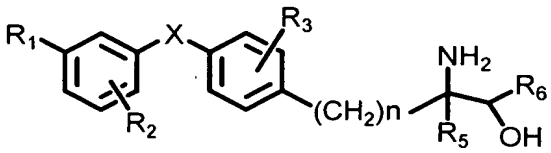
preferably at 80°C to 100°C, in a reaction solvent such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide.

Of the compounds of the general formula (1), those in which R_4 is a lower acyl group having 1 to 5 carbon atoms or a substituted or unsubstituted benzyl group are represented by the following general formula (1m):



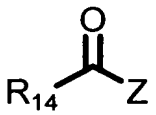
(1m)

[wherein R_1, R_2, R_3, R_5, R_6, R_{11}, X, and n are as described above]. These compounds can be obtained by the condensation of the compound represented by the following general formula (1n) with the compound represented by the following general formula (23):



(1n)

[wherein R_1, R_2, R_3, R_5, R_6, X, and n are as described above]; and



(23)

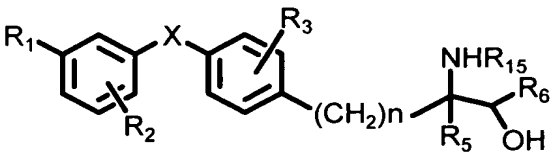
[wherein R_{14} is a lower alkyl group having 1 to 4 carbon atoms or a substituted or unsubstituted phenyl group; and Z is a

halogen atom or a hydroxyl group].

When Z in the general formula (23) is a hydroxyl group, the reaction can be carried out by using acid anhydride mixture method or active ester method, each commonly used in forming peptide bonds, and preferably involves a condensation agent. Specifically, the reaction uses a reaction solvent such as THF, DMSO, DMF, or methylene chloride and is carried out at 0°C to room temperature in the presence of an organic base such as triethylamine or pyridine, along with a condensation agent such as DCC, DIPC, DPPA, DEPC, or WSC, with DMAP optionally added as a catalyst.

When Z in the general formula (23) is a halogen atom, the reaction uses a reaction solvent such as THF, methylene chloride, or 1,4-dioxane and is carried out at 0°C to room temperature in the presence of an organic base such as triethylamine or pyridine.

Of the compounds of the general formula (1), those in which R_4 is a lower alkyl group having 1 to 4 carbon atoms or a substituted or unsubstituted benzyl group are represented by the following general formula (1o):



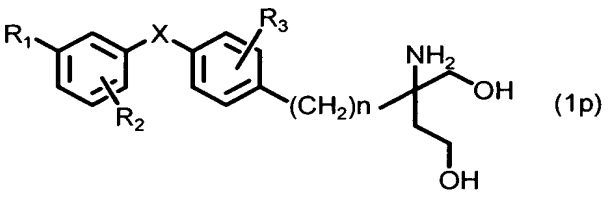
(1o)

[wherein R_{15} is a lower alkyl group having 1 to 4 carbon atoms or a substituted or unsubstituted benzyl group; and R_1, R_2, R_3,

R_5, R_6, X, and n are as described above]. These compounds can be obtained by reducing the compound of the general formula (1m).

This reaction uses a metal hydride complex, such as BH_3, $NaBH_4$, or $LiBH_4$, in particular, $LiAlH_4$, along with a reaction solvent such as THF or 1,4-dioxane. The reaction is carried out at a temperature of 0°C to refluxing temperature.

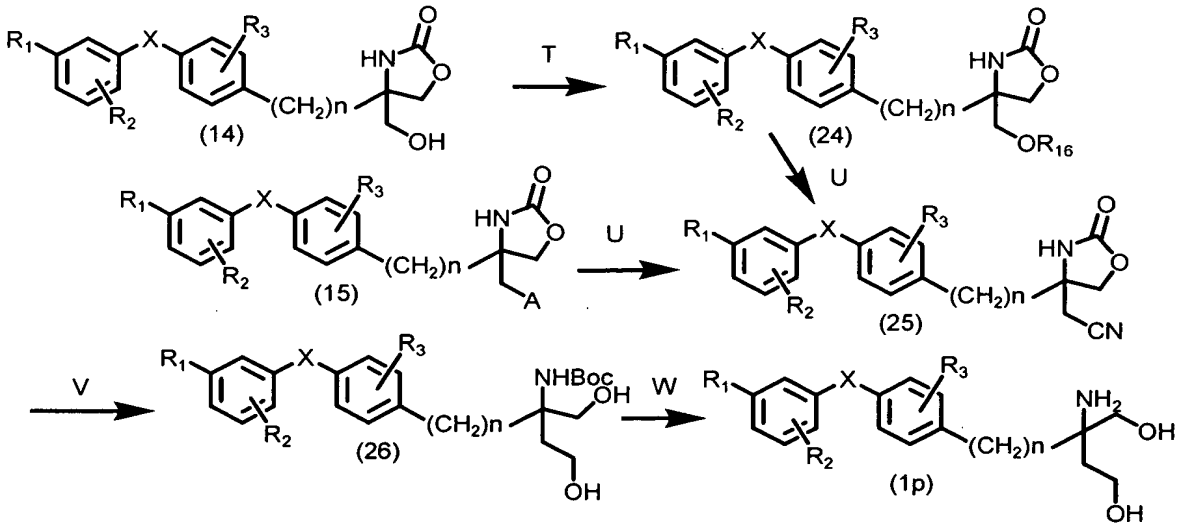
Of the compounds of the general formula (1), those in which R_5 is a hydroxyethyl group, and R_4, R_6 and R_7 are each a hydrogen atom are represented by the following general formula (1p):



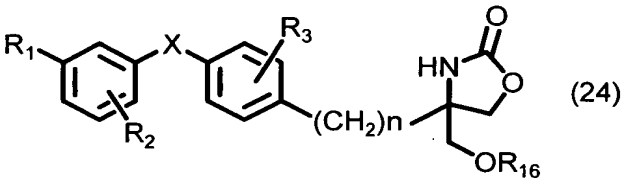
(1p)

[wherein R_1, R_2, R_3, X, and n are as described above]. These compounds can be obtained by the following synthetic pathway:

Synthetic pathway 6



In the synthetic pathway 6, the compound represented by the following general formula (24) can be obtained by reacting the compound of the general formula (14) with methanesulfonyl chloride or p-toluenesulfonyl chloride (Step T):

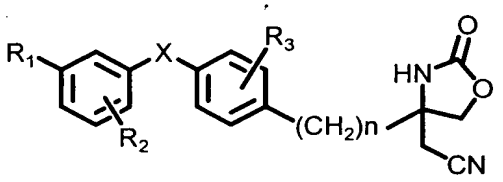


[wherein R_{16} is a methanesulfonyl or toluenesulfonyl group; and R_1, R_2, R_3, X, and n are as described above].

This reaction may be solvent-free or may use an organic solvent such as methylene chloride, chloroform, benzene, toluene, or THF and is carried out at 0°C to room temperature in the presence of an organic base such as triethylamine, diisopropylethylamine, or pyridine.

In the synthetic pathway 6, the compound represented by the following general formula (25) can be obtained by reacting

the compound of the general formula (24) with sodium cyanide or potassium cyanide (Step U):

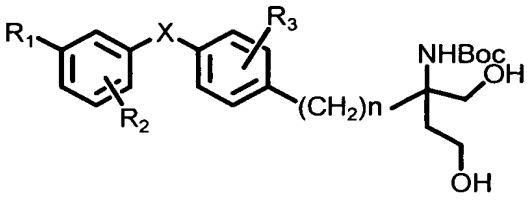


(25)

[wherein R_1, R_2, R_3, X, and n are as described above].

This reaction uses a solvent such as 1,4-dioxane, DMSO, or DMF and is carried out at room temperature to 80°C and, if necessary, in the presence of water.

In the synthetic pathway 6, the compound represented by the following general formula (26) can be obtained either by hydrolysis of the compound of the general formula (25), followed by introduction of a Boc group and reduction, or by introduction of a Boc group to the compound of the general formula (25), followed by ring-opening of the oxazolidinone ring and reduction, as shown in Step N (Step V):



(26)

[wherein R_1, R_2, R_3, Boc, X, and n are as described above].

This reaction uses a reaction solvent such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF and is carried out at 0°C to refluxing temperature, preferably at 80°C to 100°C, in the presence of a base, such as an aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide.

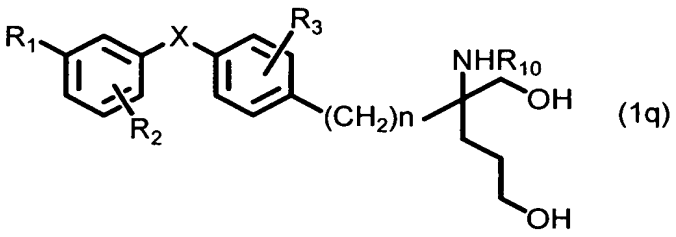
Subsequently, Boc_2O is applied at room temperature, to carry out a typical process for adding Boc group. The reaction is then carried out at 0°C to refluxing temperature in the presence of a metal hydride complex, such as BH_3, $NaBH_4$, or $LiBH_4$, in particular $LiAlH_4$, in a reaction solvent such as THF or 1,4-dioxane. Alternatively, using a reaction solvent such as THF or 1,4-dioxane, preferably acetonitrile, Boc_2O is applied at room temperature to 80°C, preferably in the presence of dimethylamino pyridine, to obtain a Boc-added form, which is followed by ring-opening of the oxazolidinone ring, carried out at room temperature in the presence of cesium carbonate in methanol as a solvent. The reaction is then carried out at 0°C to refluxing temperature in the presence of a metal hydride complex, such as BH_3, $NaBH_4$, or $LiBH_4$, in particular $LiAlH_4$, in a reaction solvent such as THF or 1,4-dioxane.

In the synthetic pathway 6, the compound represented by the general formula (1p) can be obtained by acidolysis of the compound of the general formula (26) (Step W).

This reaction is carried out at a temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate.

Of the compounds of the general formula (1), those in

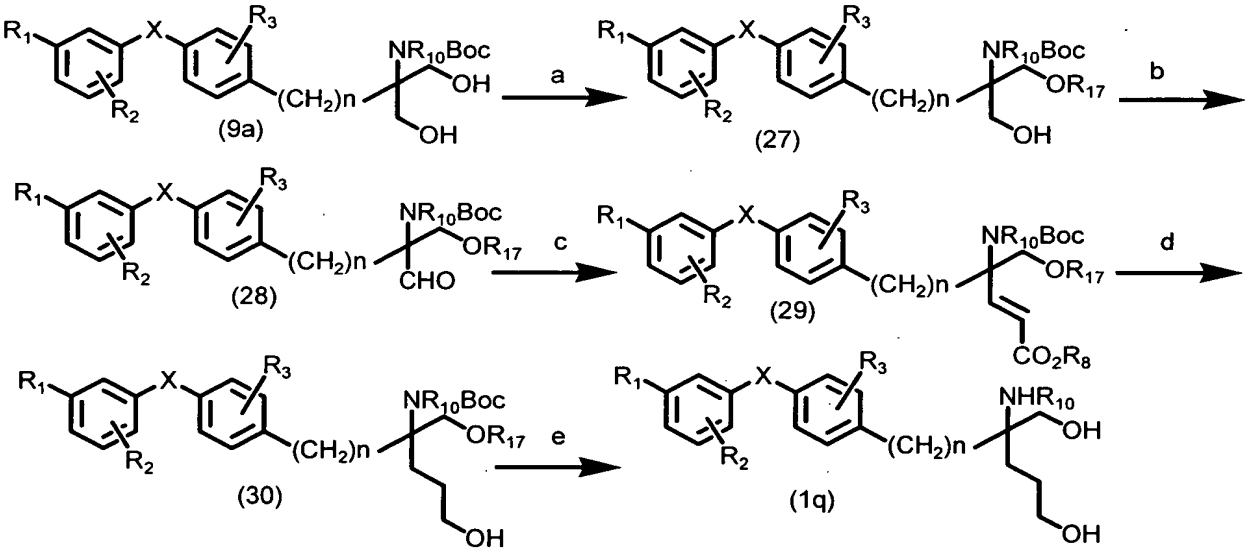
which R_5 is a hydroxypropyl group, R_4 is a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, a phenyl, or a substituted or unsubstituted benzyl group, and R_6 and R_7 are each a hydrogen atom are represented by the following general formula (1q):



(1q)

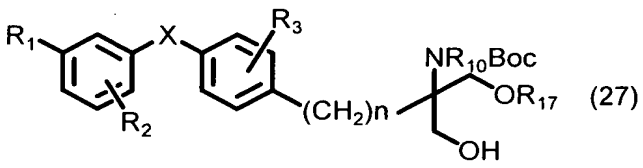
[wherein R_1, R_2, R_3, R_{10}, X, and n are as described above]. These compounds can be obtained by the following synthetic pathway:

Synthetic pathway 7



In the synthetic pathway 7, the compound represented by the following general formula (27) can be obtained by reacting the compound of the general formula (9a) with methoxymethyl

chloride, t-butyldimethylsilyl chloride, t-butyldiphenylsilyl chloride, or triisopropylsilyl chloride (Step a):

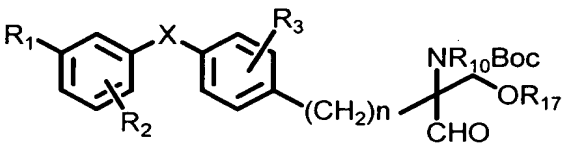


(27)

[wherein R_{17} is a methoxymethyl group, a t-butyldimethylsilyl group, a t-butyldiphenylsilyl group, or a triisopropylsilyl group; and R_1, R_2, R_3, R_{10}, Boc, X, and n are as described above].

This reaction uses an organic solvent such as acetonitrile, THF, methylene chloride, or chloroform and is carried out at 0°C to room temperature in the presence of an organic base such as triethylamine or diisopropylethylamine.

In the synthetic pathway 7, the compound represented by the following general formula (28) can be obtained by oxidation of the compound of the general formula (27) (Step b):



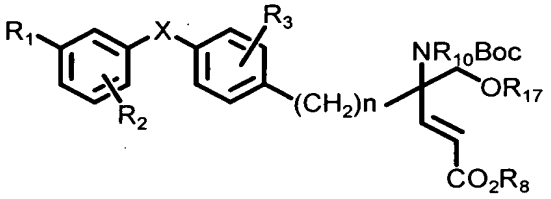
(28)

wherein R_1, R_2, R_3, R_{10}, R_{17}, Boc, X, and n are as described above.

This reaction is carried out by performing DMSO oxidation using an oxidizing agent, including chromium oxide-pyridine complex, such as pyridinium chlorochromate or pyridinium dichromate, a metal oxiding agent, such as chromium oxide,

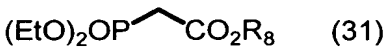
silver carbonate, or manganese dioxide, or a DMSO activating agent, such as oxalyl chloride, trifuluoroacetic anhydride, acetic anhydride, DCC and sulfur trioxide-pyridine complex.

In the synthetic pathway 7, the compound represented by the following general formula (29) can be obtained by reacting the compound of the general formula (28) with the compound represented by the following general formula (31) in the presence of a base (Step c):



(29)

[wherein R_1, R_2, R_3, R_8, R_8, R_{10}, R_{10},R_{17}, Boc, X, and n are as described above]; and

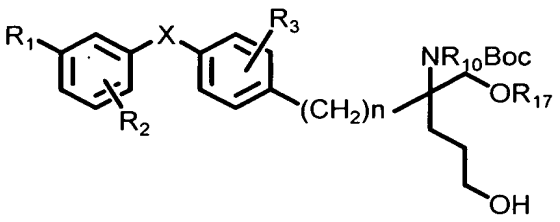


(31)

[wherein R_8 is as described above].

This reaction is carried out by first reacting the compound of the general formula (31) with a base such as sodium hydride, potassium hydride, sodium butoxide, or potassium butoxide at 0°C to room temperature in an organic solvent such as THF, DMSO, or 1,4-dioxane, and subsequently applying the compound of the general formula (29).

In the synthetic pathway 7, the compound represented by the following general formula (30) can be obtained by reducing the compound of the general formula (29) (Step d):



(30)

[wherein R_1, R_2, R_3, R_{10}, R_{17}, Boc, X, and n are as described above].

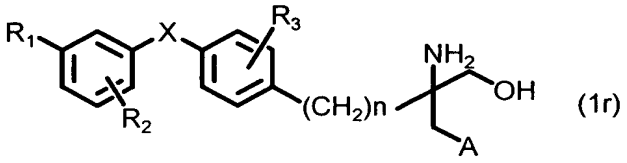
This reaction is carried out by first reducing the double bonds at room temperature to 100°C under a hydrogen pressure of atmospheric or higher pressure in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon, or ruthenium carbon, in a solvent such as ethanol, methanol, THF, DMF, or ethyl acetate. Subsequently, the ester bonds are reduced by using an alkylborane derivative, such as BH_3 or 9-BBN, or a metal hydride complex, such as $(iBu)_2AlH$, $NaBH_4$, $LiBH_4$, or $LiAlH_4$ in a reaction solvent such as 1,4-dioxane, ethanol, or methanol and, preferably, THF.

In the synthetic pathway 7, the compound represented by the general formula (1q) can be obtained by acidolysis of the compound of the general formula (30) (Step e).

When R_{17} is a silyl protective group, this reaction is carried out by first applying tetrabutylammonium fluoride or potassium fluoride in a THF solvent at 0°C to room temperature. Subsequently, the acidolysis is carried out at 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic

acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate. When R_{17} is a mehtoxymethyl protective group, the compound of the general formula (30) is directly subjected to acidolysis.

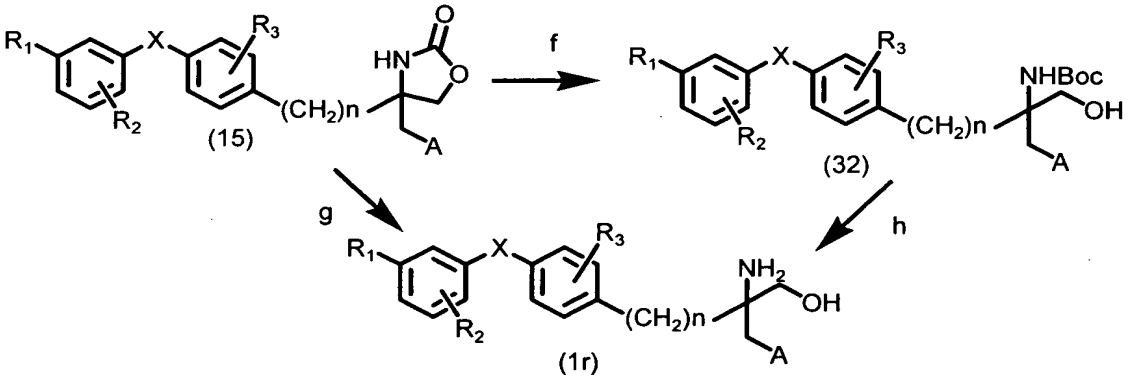
Of the compounds of the general formula (1), those in which R_5 is a monohalogenated methyl group, and R_4, R_6, and R_7 are each a hydrogen atom are represented by the following general formula (1r):



(1r)

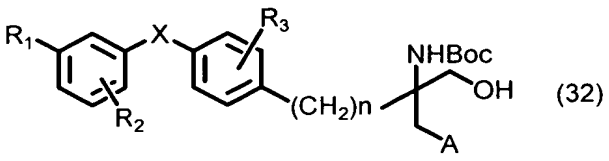
[wherein R_1, R_2, R_3, A, X, and n are as described above]. These compounds can be obtained by the following synthetic pathway:

Synthetic pathway 8



In the synthetic pathway 8, the compound represented by the following general formula (32) can be obtained by the introduction of Boc group to the compound of the general

formula (15), followed by ring-opening of the oxazolidinone ring (Step f):



(32)

[wherein R_1, R_2, R_3, A, Boc, X, and n are as described above].

This reaction uses a reaction solvent such as THF, 1,4-dioxane, or, preferably, acetonitrile and is carried out under typical conditions for Boc introduction. Preferably, Boc_2O is applied at room temperature to 80°C to obtain a Boc-added form, which is followed by ring-opening of the oxazolidinone ring, carried out at room temperature in the presence of cesium carbonate in methanol.

In the synthetic pathway 8, the compound represented by the general formula (1r) can be obtained either by acidolysis of the compound of the general formula (32) (Step h) or by hydrolysis of the compound of the general formula (15) (Step g).

The acidolysis of the compound of the general formula (32) is carried out at 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, or in a mixture with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, or ethyl acetate. The hydrolysis of the compound of the general formula (15) is

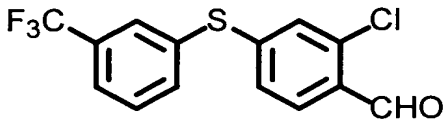
carried out at a temperature of 0°C to refluxing temperature, preferably at 80°C to 100°C, in the presence of a base, such as aqueous solution of sodium hydroxide, potassium hydroxide, or lithium hydroxide, and in a reaction solvent such as methanol, ethanol, 1,4-dioxane, DMSO, DMF, or THF.

Of the compounds represented by each general formula, those in which X is SO or SO_2 can also be obtained by oxidation of the corresponding compounds in which X is S.

This reaction uses a reaction solvent such as 1,4-dioxane, DMSO, DMF, THF, methylene chloride, or chloroform, along with an oxidizing agent such as potassium permanganate, meta-chloroperbenzoic acid, or aqueous hydrogen peroxide, and icarried out at 0°C to refluxing temperature and, preferably, at room temperature.

<Reference Example 1>

2-chloro-4-[(3-trifluoromethyl)phenylthio]benzaldehyde



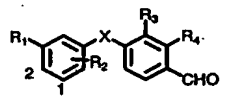
To a DMF solution (20mL) of 2-chloro-4-fluorobenzaldehyde (1.15g) and 3-(trifluoromethyl)thiophenol (1.33g), potassium carbonate (2.76g) was added and the mixture was stirred at 120°C for 1 hour while heated. The reaction mixture was poured into water and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous

solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10: 1). This gave the desired product as a pale yellow oil (1.96g).

<Reference Examples 2 through 32>

Similarly, different thiophenols and phenols were used to synthesize the different compounds shown in Table 1 below.

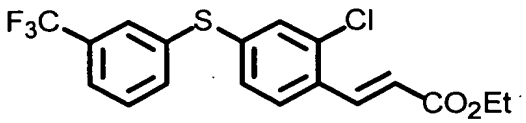
Table 1



Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
2	Cl	1-Cl	H	Cl	O	17	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O
3	t-Bu	1-H	H	H	O	18	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O
4	CF_3	1-H	H	H	O	19	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O
5	CF_3	1-H	OMe	H	O	20	i-PrO	1-iPr	H	Cl	O
6	CF_3	1-H	H	OMe	O	21	PhO	1-H	H	Cl	O
7	CF_3	1-H	H	OCH_2Ph	O	22	$PhCH_2O$	1-H	H	H	O
8	CF_3	1-H	CF_3	H	O	23	$PhCH_2O$	1-H	H	Br	O
9	CF_3	1-H	H	CF_3	O	24	$PhCH_2O$	1-H	H	SMe	O
10	CF_3	1-CF_3	H	H	O	25	$PhCH_2O$	1-H	H	Me	O
11	CF_3	1-CF_3	H	Cl	O	26	$PhCH_2O$	1-H	H	Et	O
12	CF_3	2-Cl	H	H	O	27	MeO	1-CF_3	H	H	O
13	CF_3	1-MeO	H	Cl	O	28	MeS	1-H	H	H	O
14	$Ph(CH_2)_2$	1-H	H	Cl	O	29	Cl	1-Cl	H	H	S
15	$Ph(CH_2)_2$	1-H	H	CF_3	O	30	CF_3	1-CF_3	H	Cl	S
16	$Ph(CH_2)_2$	1-CF_3	H	H	O	31	MeO	1-H	H	Cl	S

<Reference Example 32>

Ethyl 2'-chloro-4'-[(3-trifluoromethyl)phenylthio] cinnamate



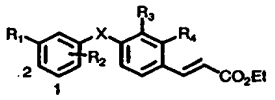
At 0°C and under a stream of argon gas, 60% sodium hydride (272mg) was added to a THF solution (30mL) of diethylphosphono ethyl acetate (1.35mL). The mixture was

stirred for 30min and a THF solution (15mL) of the compound of Reference Example 1 (1.96g) was added dropwise. The mixture was stirred for 2 hours while kept at the same temperature, which was followed by addition of water and extraction with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10: 1). This gave the desired product as a colorless oil (1.72g).

<Reference Examples 33 through 62>

Similarly, the compounds of Reference Examples 2 through 31 were used to synthesize the compounds shown in Table 2 below.

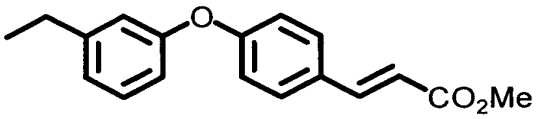
Table 2



Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
33	Cl	1-Cl	H	Cl	O	48	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O
34	t-Bu	1-H	H	H	O	49	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O
35	CF_3	1-H	H	H	O	50	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O
36	CF_3	1-H	OMe	H	O	51	i-PrO	1-iPr	H	Cl	O
37	CF_3	1-H	H	OMe	O	52	PhO	1-H	H	Cl	O
38	CF_3	1-H	H	OCH_2Ph	O	53	$PhCH_2O$	1-H	H	H	O
39	CF_3	1-H	CF_3	H	O	54	$PhCH_2O$	1-H	H	Br	O
40	CF_3	1-H	H	CF_3	O	55	$PhCH_2O$	1-H	H	SMe	O
41	CF_3	1-CF_3	H	H	O	56	$PhCH_2O$	1-H	H	Me	O
42	CF_3	1-CF_3	H	Cl	O	57	$PhCH_2O$	1-H	H	Et	O
43	CF_3	2-Cl	H	H	O	58	MeO	1-CF_3	H	H	O
44	CF_3	1-MeO	H	Cl	O	59	MeS	1-H	H	H	O
45	$Ph(CH_2)_2$	1-H	H	Cl	O	60	Cl	1-Cl	H	H	S
46	$Ph(CH_2)_2$	1-H	H	CF_3	O	61	CF_3	1-CF_3	H	Cl	S
47	$Ph(CH_2)_2$	1-CF_3	H	H	O	62	MeO	1-H	H	Cl	S

<Reference Example 63>

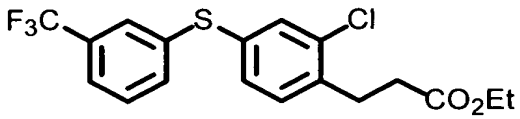
Methyl 4'-(3-ethylphenoxy)cinnamate



To a DMF solution (50mL) of 3-ethylphenol (1.13g) and methyl 4'-fluorocinnamate (834mg), potassium carbonate (1.92g) was added and the mixture was stirred at 140°C for 8 hour while heated. The reaction mixture was poured into water and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 30: 1). This gave the desired product as a yellow oil (540mg).

<Reference Example 64>

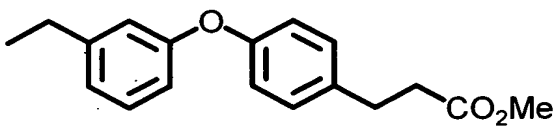
Ethyl 2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamate



The compound of Reference Example 32 (1.72g) was dissolved in ethanol (70mL). While the solution was stirred at 0°C, bismuth chloride (703mg) was added. Subsequently, sodium borohydride (673mg) was added in small portions and the mixture was stirred for 1 hour at this temperature and 3 hours at room temperature. Ice water was added and the separated insoluble inorganic residue was removed by filtration through Celite. The filtrate was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a colorless oil (1.50g) (Process A).

<Reference Example 65>

Methyl 4'-(3-ethylphenoxy)dihydrocinnamate

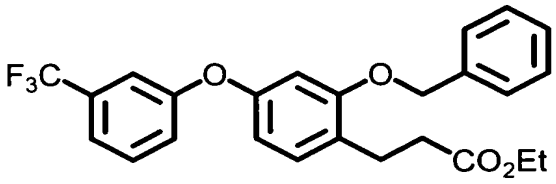


The compound of Reference Example 63 (540mg) was dissolved in ethanol (20mL) and 10%-Pd/C (80.0mg) was added.

Under hydrogen, the mixture was stirred at room temperature for 3 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give the desired product as a colorless oil (Process B).

<Reference Example 66>

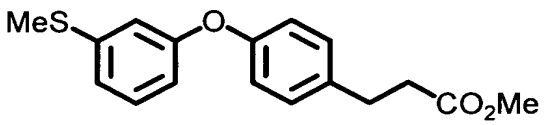
Ethyl 2'-benzyloxy-4'-[(3-trifluoromethyl)phenoxy]dihydrocinnamate



The compound of Reference Example 38 (2.29g) was dissolved in ethyl acetate (30mL) and 5%-Pd/C-ethylenediamine complex (230mg) was added. Under hydrogen, the mixture was stirred at room temperature for 3.5 hours. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give the desired product as a pale yellow oil (2.30g) (Process C).

<Reference Example 67>

Methyl 4'-[(3-methylthio)phenoxy]dihydrocinnamate



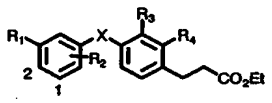
Under argon gas, the compound of Reference Example 59 (4.07g) was dissolved in methanol (50mL). While the solution

was stirred at 10°C, magnesium (1.00g) was added. The mixture was stirred for 3 hours while kept at this temperature, and diluted hydrochloric acid was added. The mixture was extracted with ethyl acetate and was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a colorless oil (3.70g) (Process D).

<Reference Examples 68 through 95>

Similarly, the compounds of Reference Examples 33 through 37, 39 through 58, and 60 through 62 were used to synthesize the compounds shown in Table 3 below.

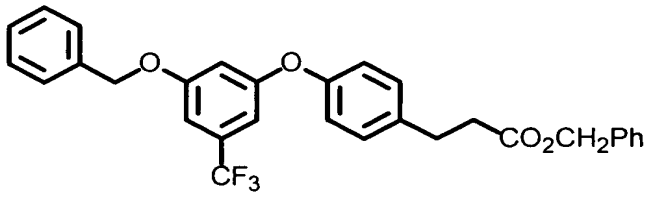
Table 3



Reference Examples	R1	R2	R3	R4	X	Process	Reference Examples	R1	R2	R3	R4	X	Process
68	Cl	1-Cl	H	Cl	O	A	82	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O	B
69	t-Bu	1-H	H	H	O	B	83	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O	B
70	CF_3	1-H	H	H	O	B	84	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O	A
71	CF_3	1-H	OMe	H	O	B	85	i-PrO	1-iPr	H	Cl	O	C
72	CF_3	1-H	H	OMe	O	B	86	PhO	1-H	H	Cl	O	A
73	CF_3	1-H	CF_3	H	O	B	87	$PhCH_2O$	1-H	H	H	O	A
74	CF_3	1-H	H	CF_3	O	B	88	$PhCH_2O$	1-H	H	Br	O	A
75	CF_3	1-CF_3	H	H	O	B	89	$PhCH_2O$	1-H	H	SMe	O	A
76	CF_3	1-CF_3	H	Cl	O	B	90	$PhCH_2O$	1-H	H	Me	O	A
77	CF_3	2-Cl	H	H	O	A	91	$PhCH_2O$	1-H	H	Et	O	A
78	CF_3	1-MeO	H	Cl	O	B	92	MeO	1-CF_3	H	H	O	A
79	$Ph(CH_2)_2$	1-H	H	Cl	O	A	93	Cl	1-H	H	H	S	D
80	$Ph(CH_2)_2$	1-H	H	CF_3	O	B	94	CF_3	1-CF_3	H	Cl	S	A
81	$Ph(CH_2)_2$	1-CF_3	H	H	O	B	95	MeO	1-H	H	Cl	S	A

<Reference Example 96>

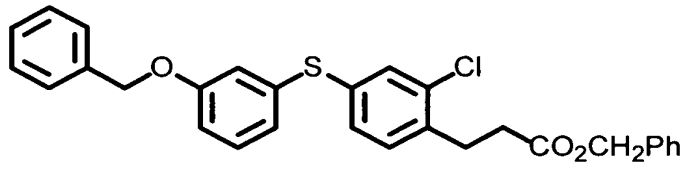
Benzyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy]dihydrocinnamate



The compound of Reference Example 92 (840mg) was dissolved in methylene chloride (20mL). While the solution was stirred at 0°C, a 1mol/L methylene chloride solution of tribromoboron (3.42mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. Subsequently, ice water was added, and the mixture was extracted with ethyl acetate and was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to give 4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate as a pale brown powder (750mg). The resulting powder was dissolved in DMF (50mL). To this solution, potassium carbonate (1.04g) and benzyl bromide (0.602mL) were added and the mixture was stirred at room temperature for 8 hours. Subsequently, the reaction mixture was poured into ice water, and the mixture was extracted with ethyl acetate and was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a brown oil.

<Reference Example 97>

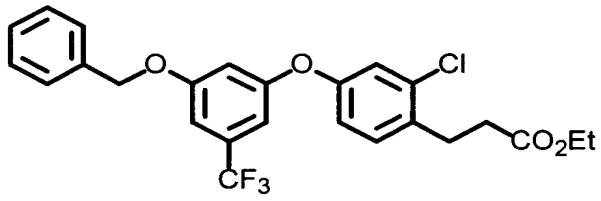
Benzyl 4'-(3-benzyloxyphenylthio)-2'-chlorodihydrocinnamate



In the same manner as in Reference Example 96, the compound of Reference Example 95 was used to give the desired product as a yellow oil.

<Reference Example 98>

Ethyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy]-2'-chlorodihydrocinnamate

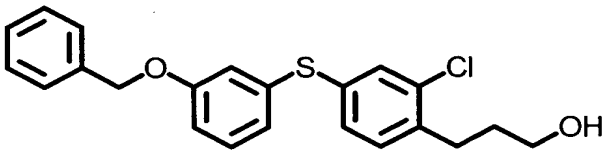


In the same manner as in Reference Example 96, the compound of Reference Example 78 was reacted to give 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate. This product (1.47g) was dissolved in ethanol (10mL). While this solution was stirred at 0°C, thionyl chloride (3mL) was added dropwise. The mixture was stirred for 2 hours while kept at this temperature. Subsequently, the solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10:1

and then 6:1) to give ethyl 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate as a colorless oil (1.38g). In the same manner as in Reference Example 96, the resulting ester was converted into a benzyl ether using potassium carbonate and benzyl bromide. This gave the desired product as a colorless oil.

<Reference Example 99>

4'-[(3-benzyloxy)phenylthio]-2'-chlorodihydrocinnamyl alcohol

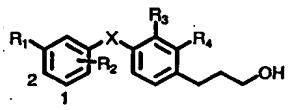


The compound of Reference Example 97 (7.40g) was dissolved in THF (100mL). While this solution was stirred at 0°C, lithium aluminum hydride (500mg) was added. After 10min, a 20% aqueous solution of NaOH was added and the separated insoluble inorganic residue was removed by filtration through Celite. The filtrate was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a colorless oil (6.37g).

<Reference Examples 100 through 130>

In a similar manner to Reference Example 99, the compounds of Reference Examples 68 through 77, 79 through 91, 93 through 94, and 96 and 98 were used to synthesize the compounds shown in Table 4 below.

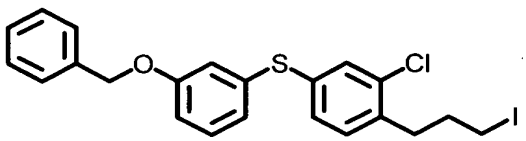
Table 4



Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
100	Cl	1-Cl	H	Cl	O	116	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O
101	t-Bu	1-H	H	H	O	117	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O
102	CF_3	1-H	H	H	O	118	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O
103	CF_3	1-H	OMe	H	O	119	i-PrO	1-iPr	H	Cl	O
104	CF_3	1-H	H	OMe	O	120	PhO	1-H	H	Cl	O
105	CF_3	1-H	CF_3	H	O	121	$PhCH_2O$	1-H	H	H	O
106	CF_3	1-H	H	CF_3	O	122	$PhCH_2O$	1-H	H	Br	O
107	CF_3	1-CF_3	H	H	O	123	$PhCH_2O$	1-H	H	SMe	O
108	CF_3	1-CF_3	H	Cl	O	124	$PhCH_2O$	1-H	H	Me	O
109	CF_3	2-Cl	H	H	O	125	$PhCH_2O$	1-H	H	Et	O
110	CF_3	$PhCH_2O$	H	Cl	O	126	$PhCH_2O$	1-CF_3	H	H	O
111	$Ph(CH_2)_2$	1-H	H	Cl	O	127	Cl	1-H	H	H	S
112	$Ph(CH_2)_2$	1-H	H	CF_3	O	128	CF_3	1-CF_3	H	Cl	S
113	$Ph(CH_2)_2$	1-CF_3	H	H	O	129	Et	1-H	H	H	O
114	CF_3	1-H	H	$PhCH_2O$	O	130	MeS	1-H	H	H	O
115	CF_3	1-H	H	Cl	S						

<Reference Example 131>

4'-(3-benzyloxyphenylthio)-2'-chloro-dihydrocinnamyl iodide



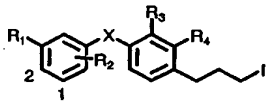
The compound of Reference Example 99 (1.38g) was dissolved in THF (20mL). While this solution was stirred at 0°C, imidazole (545mg), triphenylphosphine (2.10g), and iodine (2.00g) were added. The mixture was stirred for 2 hours at this temperature and for the subsequent 1.5 hours at room temperature, and additional imidazole (160mg), triphenyl

phosphine (600mg), and iodine (500mg) were added. The mixture was stirred overnight, followed by the addition of water and then sodium thiosulfate. The reaction mixture was then extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 50:1) to give the desired product as a colorless oil (1.55g).

<Reference Examples 132 through 162>

In a similar manner to Reference Example 131, the compounds of Reference Examples 100 through 130 were used to synthesize the compounds shown in Table 5 below.

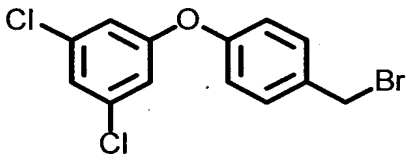
Table 5



Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
132	Cl	1-Cl	H	Cl	O	148	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O
133	t-Bu	1-H	H	H	O	149	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O
134	CF_3	1-H	H	H	O	150	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O
135	CF_3	1-H	OMe	H	O	151	i-PrO	1-IPr	H	Cl	O
136	CF_3	1-H	H	OMe	O	152	PhO	1-H	H	Cl	O
137	CF_3	1-H	CF_3	H	O	153	$PhCH_2O$	1-H	H	H	O
138	CF_3	1-H	H	CF_3	O	154	$PhCH_2O$	1-H	H	Br	O
139	CF_3	1-CF_3	H	H	O	155	$PhCH_2O$	1-H	H	SMe	O
140	CF_3	1-CF_3	H	Cl	O	156	$PhCH_2O$	1-H	H	Me	O
141	CF_3	2-Cl	H	H	O	157	$PhCH_2O$	1-H	H	Et	O
142	CF_3	$PhCH_2O$	H	Cl	O	158	$PhCH_2O$	1-CF_3	H	H	O
143	$Ph(CH_2)_2$	1-H	H	Cl	O	159	Cl	1-H	H	H	S
144	$Ph(CH_2)_2$	1-H	H	CF_3	O	160	CF_3	1-CF_3	H	Cl	S
145	$Ph(CH_2)_2$	1-CF_3	H	H	O	161	Et	1-H	H	H	O
146	CF_3	1-H	H	$PhCH_2O$	O	162	MeS	1-H	H	H	O
147	CF_3	1-H	H	Cl	S						

<Reference Example 163>

4-(3,5-dichlorophenoxy)benzylbromide

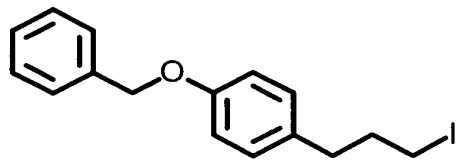


Using 3,5-dichlorophenol and 4-fluorobenzaldehyde, the reaction was carried out in the same manner as in Reference Example 1 to obtain 4-(3,5-dichlorophenoxy)benzaldehyde. Subsequently, the same procedure as in Reference Example 99 was followed using sodium borohydride in place of the lithium aluminum hydride. This gave 4-(3,5-dichlorophenoxy)benzyl alcohol. The resulting alcohol (2.03g), along with carbon tetrabromide (2.75g), was dissolved in methylene chloride (30mL). While this solution was stirred at 0°C, triphenyl phosphine (2.17g) was added. The mixture was stirred at 0°C

for 1 hour and at room temperature for the subsequent 30min. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 20:1) to give the desired product as a colorless oil (3.12g).

<Reference Example 164>

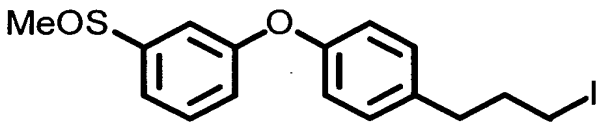
4'-benzyloxy-dihydrocinnamyl iodide



Using 4'-benzyloxydihydrocinnamyl alcohol, the reaction was carried out in the same manner as in Reference Example 131 to obtain the desired product as a yellow powder.

<Reference Example 165>

1-iodopropyl-4-[(3-methanesulfinyl)phenoxy]benzene

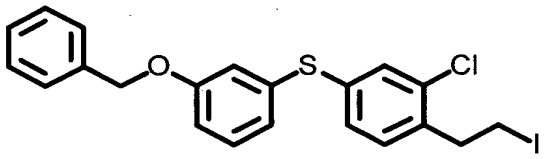


The compound of Reference Example 162 (1.80g) was dissolved in methylene chloride (30mL). While this solution was stirred at 0°C, m-chloroperbenzoic acid (770mg) was added in small portions. The mixture was stirred at this temperature for 1 hour and at room temperature for the subsequent 24 hours. Following addition of water, the mixture was extracted with

ethyl acetate and the extract was washed sequentially with a saturated aqueous solution of sodium carbonate and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 2:1 and then 1:2) to give the desired product as a yellow oil (1.29g).

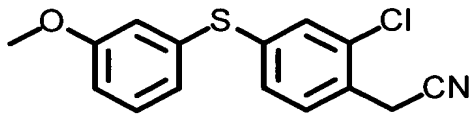
<Reference Example 166>

4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl iodide



<Reference Example 166-1>

2'-chloro-4'-(3-methoxyphenylthio)benzylcyanide

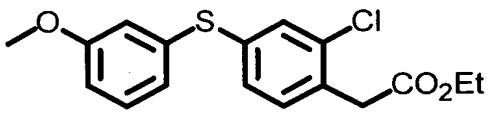


The compound of Reference Example 31 was treated in the same manner as in Reference Example 99 to obtain an alcohol. The alcohol (5.64g) was dissolved in methylene chloride (100mL) and phosphorus tribromide (2.25mL) was added dropwise. Following stirring at room temperature for 1 hour, ice water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and an aqueous

solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed to obtain a pale yellow oil. The oil and potassium cyanide (1.56g) were dissolved in a mixture of DMSO (25mL) and water (10mL) and the solution was stirred at 90°C for 5 hours. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10:1) to give the desired cyano-product as a pale yellow oil (3.81g).

<Reference Example 166-2>

2'-chloro-4'-(3-methoxyphenylthio)phenylethyl acetate



The cyano-product (3.81g) and potassium hydroxide (3.68g) were added to a mixture of ethanol (80mL), and water (10mL), and the solution was refluxed for 6 hours. Subsequently, the solution was allowed to cool and the insoluble material was removed by filtration. The filtrate was neutralized with diluted hydrochloric acid. This mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The

organic phase was then dried over anhydrous sodium sulfate. The solvent was removed and ethanol (50mL) and thionyl chloride (2mL) were added to the resulting residue. This mixture was stirred at room temperature for 1 hour and the solvent was removed. The resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10:1) to give the ethyl ester product as a colorless oil (3.89g).

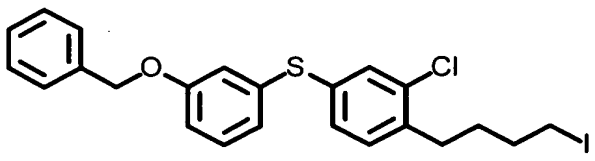
<Reference Example 166-3>

4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl iodide

The ethyl ester was reacted in the same manner as in Reference Example 98 to obtain 4'-(3-benzyloxyphenylthio)-2'-chlorophenylethyl acetate. The product was reduced as in Reference Example 99 to obtain an alcohol, which in turn was reacted in the same manner as in Reference Example 131 to give the desired product as a colorless oil.

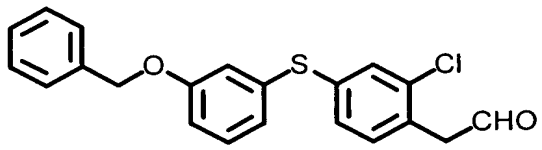
<Reference Example 167>

1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutylbenzene



<Reference Example 167-1>

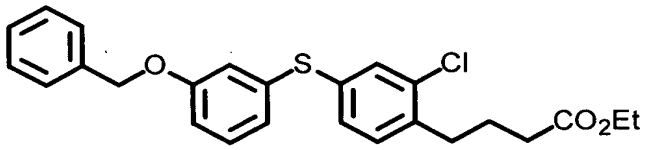
4-(3-benzyloxyphenylthio)-2-chlorophenethyl aldehyde



4'-(3-benzyloxyphenylthio)-2'-chlorophenylethyl acetate obtained in Reference Example 166-3 was subjected to alkali-hydrolysis. The resulting product was condensed with N,O-dimethylhydroxylamine to form an amide product, which in turn was reduced in the same manner as in Reference Example 99 to give the desired aldehyde product as a yellow oil.

<Reference Example 167-2>

4-[(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl butyrate



The compound of Reference Example 167-1 was reacted in the same manner as in Reference Example 32 and the unsaturated bonds of the resulting product were reduced in the same manner as in Reference Example 64 to give the desired ethyl butyrate derivative.

<Reference Example 167-3>

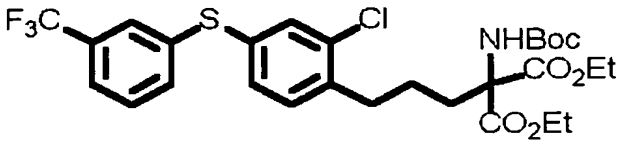
1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutylbenzene

The compound of Reference Example 167-2 was reacted in the same manner as in Reference Example 99 to obtain an

alcohol product, which in turn was reacted in the same manner as in Reference Example 131 to give the desired product as a colorless oil.

<Example 1>

Ethyl 2-t-butoxycarbonylamino-5-[2-chloro-4-(3-trifluoromethylphenylthio)]phenyl-2-ethoxycarbonylpentanoate



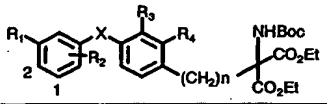
At room temperature and under argon gas, sodium t-butoxide (490mg) was added to diethyl 2-t-butoxycarbonylaminomalonate (1.3mL) in a mixture of THF (35mL) and DMF (4mL). This mixture was stirred at 80°C for 20min and was allowed to cool to room temperature. To the cooled mixture, a THF solution (5mL) of the compound of Reference Example 147 (1.55g) was added dropwise. The resulting mixture was refluxed for 5 hours, was poured into ice water, and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 5:1) to give the desired product as a colorless oil (1.87g).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.22-1.36(6H, m), 1.42(9H, s), 1.45-1.53(2H, m), 2.37(2H, br), 2.74(2H, t, J=7.8Hz), 4.23(4H, m), 5.94(1H, s), 7.16-7.21(2H, m), 7.36-7.56(5H, m)

<Examples 2 through 36>

In a similar manner to Example 1, the compounds of Reference Examples 131 through 146, 148 through 161, and 163, 165, 166 and 167 were used to synthesize the compounds shown in Table 6 below.

Table 6

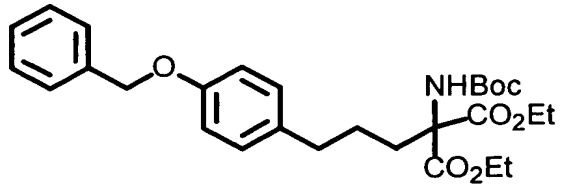


Examples	R1	R2	R3	R4	X	n	Characteristics	Yield (%)
2	Cl	1-Cl	H	Cl	O	3	Colorless oil	74
3	t-Bu	1-H	H	H	O	3	Colorless oil	64
4	CF_3	1-H	H	H	O	3	Colorless oil	100
5	CF_3	1-H	OMe	H	O	3	Colorless oil	100
6	CF_3	1-H	H	OMe	O	3	Colorless oil	100
7	CF_3	1-H	CF_3	H	O	3	Colorless oil	100
8	CF_3	1-H	H	CF_3	O	3	Colorless oil	92
9	CF_3	1-CF_3	H	H	O	3	Colorless oil	47
10	CF_3	1-CF_3	H	Cl	O	3	Colorless oil	89
11	CF_3	2-Cl	H	H	O	3	Colorless oil	94
12	CF_3	$PhCH_2O$	H	Cl	O	3	Colorless oil	91
13	$Ph(CH_2)_2$	1-H	H	Cl	O	3	Colorless oil	83
14	$Ph(CH_2)_2$	1-H	H	CF_3	O	3	Colorless oil	90
15	$Ph(CH_2)_2$	1-CF_3	H	H	O	3	Colorless oil	97
16	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O	3	Colorless oil	95
17	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O	3	Colorless oil	100
18	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O	3	Colorless oil	98
19	i-PrO	1-iPr	H	Cl	O	3	Colorless oil	100
20	PhO	1-H	H	Cl	O	3	Colorless oil	92
21	$PhCH_2O$	1-H	H	H	O	3	Colorless oil	95
22	$PhCH_2O$	1-H	H	Br	O	3	Colorless oil	100
23	$PhCH_2O$	1-H	H	SMe	O	3	Colorless oil	-
24	$PhCH_2O$	1-H	H	Me	O	3	Colorless oil	100
25	$PhCH_2O$	1-H	H	Et	O	3	Colorless oil	72
26	$PhCH_2O$	1-H	H	Cl	S	2	Pale yellow oil	100
27	$PhCH_2O$	1-H	H	Cl	S	3	Colorless oil	100
28	$PhCH_2O$	1-H	H	Cl	S	4	Colorless oil	100
29	$PhCH_2O$	1-CF_3	H	H	O	3	Colorless oil	99
30	Cl	1-H	H	H	S	3	Colorless oil	82
31	CF_3	1-CF_3	H	Cl	S	3	Colorless oil	66
32	Et	1-H	H	H	O	3	Colorless oil	100
33	SOMe	1-H	H	H	O	3	Colorless oil	100
34	Cl	1-Cl	H	H	O	1	Colorless oil	56
35	CF_3	1-H	H	$PhCH_2O$	O	3	Colorless oil	100
36	$PhCH_2O$	1-H	H	Cl	O	3	Colorless oil	100

- Yield is shown in Table 7 in association with the subsequent step.

<Example 37>

Ethyl 5-[(4-benzyloxy)phenyl]-2-t-butoxycarbonylamino-2-ethoxycarbonylpentanoate



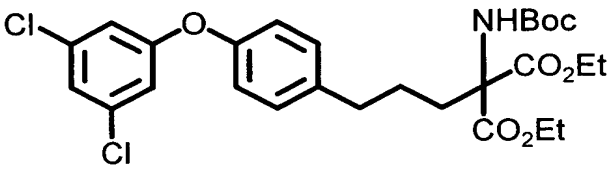
The compound of Reference Example 164 was reacted in the

same manner as in Example 1 to give the desired product as a pale yellow oil.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.22(6H, t, J=7.1Hz), 1.42(9H, s), 1.44-1.47(2H, m), 2.31(2H, br s), 2.57(2H, t, J=7.6Hz), 4.11-4.27(4H, m), 5.03(2H, s), 5.92(1H, br s), 6.88(2H, d, J=8.8Hz), 7.06(2H, d, J=8.8Hz), 7.29-7.43(5H, m)

<Example 38>

Ethyl 2-t-butoxycarbonylamino-5-[4-(3,5-dichlorophenoxy)phenyl]-2-ethoxycarbonylpentanoate

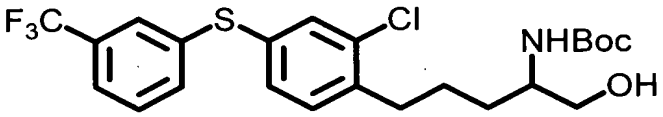


The compound of Example 37 was reduced in the same manner as in Reference Example 65. The resulting phenol product (1.27g), along with 3,5-dichlorophenylboric acid (1.18g), was dissolved in methylene chloride (30mL). While this solution was being stirred, copper acetate (676mg) and triethylamine (0.86mL) were added. After 16 hours and a further 8 hours later, the same amount of additional copper acetate was added and the mixture was stirred for the subsequent 40 hours. Subsequently, the insoluble material was removed by filtration. The filtrate was poured into water and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of

sodium chloride. The organic phase was then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 20:1) to give the desired product as a pale blue oil (333mg).

<Example 39>

2-t-butoxycarbonylamino-5-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]pentane-1-ol



The compound of Example 1 (1.87g) was dissolved in THF (30mL). While this solution was stirred at 0°C, lithium borohydride (675mg) was added. Subsequently, ethanol (5mL) was added and the mixture was allowed to gradually warm to room temperature. After stirring overnight, ice water was added to the reaction mixture and the organic solvent was removed under reduced pressure. To the resulting residue, a 10% aqueous citric acid was added to adjust the pH to 3. The resulting mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1) to give

the desired product (0.27g) as a colorless oil.

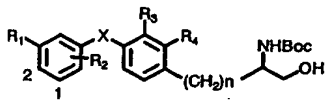
FABMS:490($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 1.63-1.73(4H, m), 2.72-2.78(2H, m), 3.57(1H, br), 3.68-3.70(2H, m), 4.61(1H, br s), 7.20-7.22(2H, m), 7.39-7.55(5H, m)

<Examples 40 through 74>

In a similar manner to Example 39, the compounds of Examples 2 through 36 and 38 were used to synthesize the compounds shown in Table 7 below.

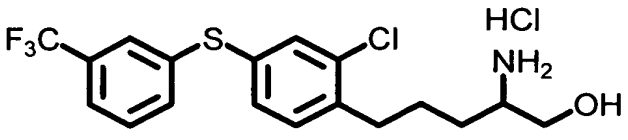
Table 7



Examples	R1	R2	R3	R4	X	n	Characteristics	Yield (%)
40	Cl	1-Cl	H	Cl	O	3	Colorless oil	12
41	t-Bu	1-H	H	H	O	3	Colorless oil	15
42	CF_3	1-H	H	H	O	3	Colorless oil	17
43	CF_3	1-H	OMe	H	O	3	Colorless oil	5
44	CF_3	1-H	H	OMe	O	3	Colorless oil	17
45	CF_3	1-H	CF_3	H	O	3	Colorless oil	16
46	CF_3	1-H	H	CF_3	O	3	Colorless oil	22
47	CF_3	1-CF_3	H	H	O	3	Colorless oil	14
48	CF_3	1-CF_3	H	Cl	O	3	Colorless oil	19
49	CF_3	2-Cl	H	H	O	3	Colorless powder	29
50	CF_3	$PhCH_2O$	H	Cl	O	3	Colorless oil	12
51	$Ph(CH_2)_2$	1-H	H	Cl	O	3	Colorless oil	15
52	$Ph(CH_2)_2$	1-H	H	CF_3	O	3	Colorless oil	18
53	$Ph(CH_2)_2$	1-CF_3	H	H	O	3	Colorless oil	16
54	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O	3	Colorless oil	11
55	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O	3	Colorless oil	13
56	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O	3	Colorless oil	10
57	i-PrO	1-iPr	H	Cl	O	3	Colorless oil	7
58	PhO	1-H	H	Cl	O	3	Colorless oil	17
59	$PhCH_2O$	1-H	H	H	O	3	Colorless oil	11
60	$PhCH_2O$	1-H	H	Br	O	3	Colorless oil	11
61	$PhCH_2O$	1-H	H	SMe	O	3	Colorless oil	10
62	$PhCH_2O$	1-H	H	Me	O	3	Colorless oil	11
63	$PhCH_2O$	1-H	H	Et	O	3	Colorless oil	8
64	$PhCH_2O$	1-H	H	Cl	S	2	Pale yellow oil	11
65	$PhCH_2O$	1-H	H	Cl	S	3	Colorless oil	26
66	$PhCH_2O$	1-H	H	Cl	S	4	Colorless oil	15
67	$PhCH_2O$	1-CF_3	H	H	O	3	Colorless oil	10
68	Cl	1-H	H	H	S	3	Colorless oil	31
69	CF_3	1-CF_3	H	Cl	S	3	Colorless oil	13
70	Et	1-H	H	H	O	3	Colorless oil	13
71	SOMe	1-H	H	H	O	3	Colorless oil	27
72	Cl	1-Cl	H	H	O	1	Colorless powder	24
73	CF_3	1-H	H	$PhCH_2O$	O	3	Colorless oil	5
74	Cl	1-Cl	H	H	O	3	Colorless oil	13
75	$PhCH_2O$	1-H	H	Cl	O	3	Colorless oil	19

<Example 76>

2-amino-5-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]pentane-1-ol hydrochloride



To a methanol solution (5mL) of the compound of Example 39 (0.27g), ethyl acetate containing 3mol/L hydrochloric acid

(5mL) was added and the mixture was stirred in an ice bath. The mixture was allowed to warm to room temperature and was left overnight. Subsequently, the solvent was removed under reduced pressure to give the desired product as a colorless powder (0.22g).

FABMS: 390 ($[M+H]^+$)

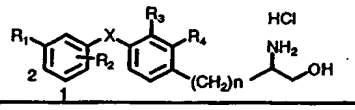
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.52-1.61(4H, br s), 2.70(2H, t, J=7.3Hz), 3.09(1H, br), 3.38-3.43(1H, m), 3.55-3.58(1H, m), 5.28(1H, t, J=4.9Hz), 7.34(1H, dd, J=7.9Hz, 2.0Hz), 7.41(1H, d, J=7.3Hz), 7.54(1H, d, J=2.0Hz), 7.56-7.63(3H, m), 7.68(1H, d, J=7.3Hz), 7.80(3H, br)

MP = 166-168°C

<Example 77-111>

In a similar manner to Example 36, the compounds shown in Table 7 were used to synthesize the compounds shown in Table 8 below.

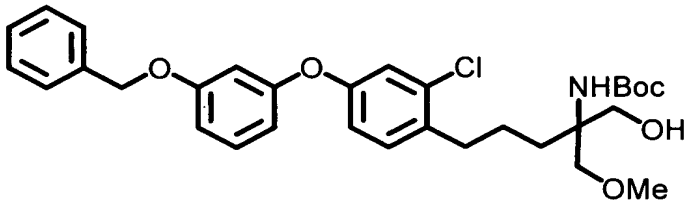
Table 8



Examples	R1	R2	R3	R4	X	n	Characteristics	Yield (%)	FABMS $[M+H]^+$	Melting point (℃)
77	Cl	1-Cl	H	Cl	O	3	Colorless powder	87	374	154-156
78	t-Bu	1-H	H	H	O	3	Colorless powder	98	328	133-137
79	CF_3	1-H	H	H	O	3	Colorless powder	100	340	143-145
80	CF_3	1-H	OMe	H	O	3	Colorless amorphous	100	370	
81	CF_3	1-H	H	OMe	O	3	Colorless oil	88	370	
82	CF_3	1-H	CF_3	H	O	3	Colorless powder	91	408	128-130
83	CF_3	1-H	H	CF_3	O	3	Colorless amorphous	95	408	
84	CF_3	1-CF_3	H	H	O	3	Colorless powder	88	408	122-125
85	CF_3	1-CF_3	H	Cl	O	3	Colorless powder	68	442	126-128
86	CF_3	2-Cl	H	H	O	3	Pale yellow amorphous	87	374	
87	CF_3	$PhCH_2O$	H	Cl	O	3	Colorless amorphous	92	480	
88	$Ph(CH_2)_2$	1-H	H	Cl	O	3	Pale yellow amorphous	87	410	
89	$Ph(CH_2)_2$	1-H	H	CF_3	O	3	Colorless amorphous	91	444	
90	$Ph(CH_2)_2$	1-CF_3	H	H	O	3	Colorless amorphous	94	444	
91	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	H	O	3	Colorless oil	98	480	
92	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	CF_3	O	3	Colorless oil	100	548	
93	$Ph(CH_2)_2$	1-$Ph(CH_2)_2$	H	Cl	O	3	Yellow oil	95	514	
94	i-PrO	1-iPr	H	Cl	O	3	Colorless amorphous	82	406	
95	PhO	1-H	H	Cl	O	3	Brown amorphous	89	398	
96	$PhCH_2O$	1-H	H	H	O	3	Colorless amorphous	100	378	
97	$PhCH_2O$	1-H	H	Br	O	3	Colorless amorphous	92	458	
98	$PhCH_2O$	1-H	H	SMe	O	3	Yellow oil	96	424	
99	$PhCH_2O$	1-H	H	Me	O	3	Yellow amorphous	89	392	
100	$PhCH_2O$	1-H	H	Et	O	3	Yellow amorphous	64	406	
101	$PhCH_2O$	1-H	H	Cl	S	2	Colorless amorphous	93	414	
102	$PhCH_2O$	1-H	H	Cl	S	3	Colorless powder	100	428	145-147
103	$PhCH_2O$	1-H	H	Cl	S	4	Colorless amorphous	93	442	
104	$PhCH_2O$	1-CF_3	H	H	O	3	Colorless amorphous	93	446	
105	Cl	1-H	H	H	S	3	Colorless powder	71	322	122-124
106	CF_3	1-CF_3	H	Cl	S	3	Colorless powder	92	458	134-137
107	Et	1-H	H	H	O	3	Colorless powder	91	300	117-118
108	SOMe	1-H	H	H	O	3	Colorless powder	100	334	110-112
109	Cl	1-Cl	H	H	O	1	Colorless powder	96	312	157-160
110	CF_3	1-H	H	$PhCH_2O$	O	3	Colorless oil	100	446	
111	Cl	1-Cl	H	H	O	3	Colorless powder	92	340	138-140

<Example 112>

5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethylpentane-1-ol



2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-2-t-

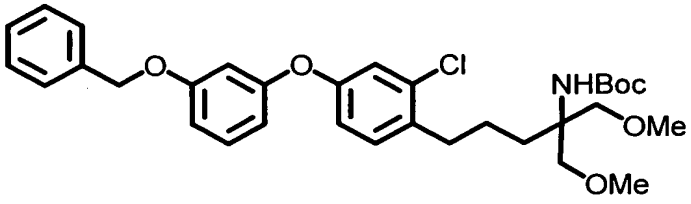
butoxycarbonylamino-1,3-propanediol (720mg) was dissolved in acetonitrile (20mL). Ag_2O (1.85g) and MeI (3mL) were added and the mixture was stirred at room temperature for 7 days. Subsequently, the mixture was filtered through Celite and the filtrate was concentrated and purified on a silica gel column chromatography (hexane: ethyl acetate = 3:1). The dimethyl ether product (Example 112, 360mg) and the monomethyl ether product (Example 113, 310mg), each a colorless oil, were obtained from the first eluate fraction and the second eluate fraction, respectively.

FABMS: 556 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.48-1.81(4H, m), 2.68(2H, t, J=7.8Hz), 3.33(1H, d, J=8.8Hz), 3.36(3H, s), 3.57(1H, d, 8.8Hz), 3.65(2H, d, J=6.8Hz), 5.03(2H, s), 5.10(1H, br s), 6.59-6.62(2H, m), 6.74(1H, dd, J=8.3Hz, 2.4Hz), 6.84(1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.15(1H, d, J=8.3Hz), 7.23(1H, t, J=8.3Hz), 7.33-7.42(5H, m)

<Example 113>

2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-2-t-butoxycarbonylamino-1,3-propanedioldimethyl ether



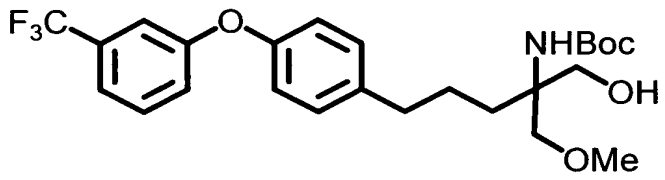
A colorless oil (See Example 112).

FABMS: 570 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.42(9H, s), 1.48-1.61(3H, m), 1.84(1H, br), 2.67(2H, t, J=7.8Hz), 3.34(6H, s), 3.46(2H, d, J=8.8Hz), 3.50(2H, d, J=8.8Hz), 4.82(1H, br s), 5.03(2H, s), 6.59-6.63(2H, m), 6.73(1H, dd, J=8.3Hz, 2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.99(1H, d, J=2.4Hz), 7.15(1H, d, J=8.3Hz), 7.23(1H, t, J=8.3Hz), 7.32-7.42(5H, m)

<Example 114>

2-t-butoxycarbonylamino-2-methoxymethyl-5-[4-(3-trifluoromethylphenoxy)phenyl]pentane-1-ol



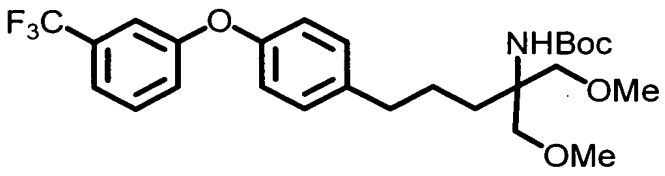
2-t-butoxycarbonylamino-2-[4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol was reacted in the same manner as in Example 112 to give the desired products (Example 114 and Example 115), each as a colorless oil.

FABMS: 484 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.42(9H, s), 1.48-1.83(4H, m), 2.57-2.65(2H, m), 3.33(1H, d, J=8.8Hz), 3.37(3H, s), 3.58(1H, d, 8.8Hz), 3.62(2H, br s), 5.07(1H, br s), 6.94(2H, d, J=6.4Hz), 7.10-7.21(4H, m), 7.30(1H, d, J=7.8Hz), 7.40(1H, t, J=7.8Hz)

<Example 115>

2-t-butoxycarbonylamino-2-[4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanedioldimethyl ether



A colorless oil (See Example 114).

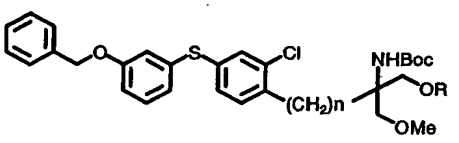
FABMS: 498 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.42(9H, s), 1.48-1.66(3H, m), 1.81-1.85(1H, m), 2.60(2H, t, J=7.8Hz), 3.34(6H, s), 3.46(2H, d, J=8.8Hz), 3.49(2H, d, 8.8Hz), 4.83(1H, br s), 6.93(2H, dd, J=6.4Hz, 2.0Hz), 7.12-7.22(4H, m), 7.31(1H, d, J=7.8Hz), 7.41(1H, d, J=7.8Hz)

<Example 116-119>

Using 2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-2-t-butoxycarbonylamino-1,3-propanediol and 2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-2-t-butoxycarbonylamino-1,3-propanediol, reactions were carried out in the same manner as in Example 112 to obtain the compounds shown in Table 9 below.

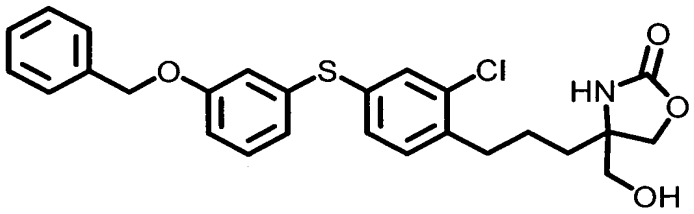
Table 9



Examples	R	n	Characteristics	FABMS $[M+H]^+$
116	H	2	Colorless oil	558
117	Me	2	Colorless oil	572
118	H	3	Colorless oil	572
119	Me	3	Colorless oil	586

<Example 120>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-hydroxymethyl-2-oxazolidinone

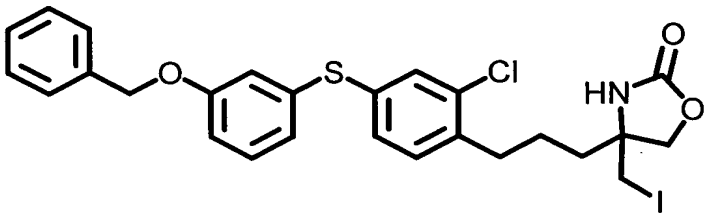


2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-2-t-butoxycarbonylamino-1,3-propanediol (3.30g) was dissolved in THF (80mL). At 0°C, 60% sodium hydride (600mg) was added and the mixture was stirred at room temperature for 24 hours. To the resulting reaction mixture, ice water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium hydroxide, and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1 and then ethyl acetate alone) to give the desired product as a pale yellow oil (2.37g).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.63-1.72(4H, m), 2.74(2H, t, J=6.8Hz), 3.51(1H, d, J=11.2Hz), 3.58(1H, d, J=11.2Hz), 4.09(1H, d, J=8.8Hz), 4.24(1H, d, J=8.8Hz), 5.02(2H, s), 5.28(1H, br s), 6.87-6.90(1H, m), 6.94-7.00(2H, m), 7.09-7.16(2H, m), 7.22-7.52(7H, m)

<Example 121>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-iodomethyl-2-oxazolidinone



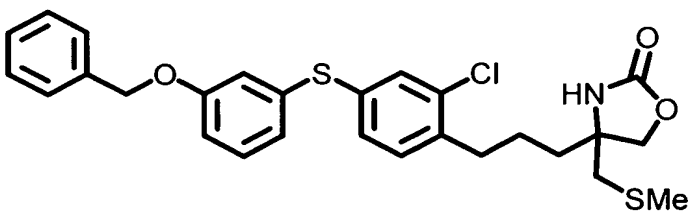
To a pyridine solution (30mL) of the compound of Example 120 (2.37g), p-toluenesulfonyl chloride (1.33g) was added and the mixture was stirred at room temperature for 24 hours and at 60°C for the subsequent 5 hours. Subsequently, water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water, diluted hydrochloric acid, water and then a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1) to give the sulfonate product as a colorless oil (2.14g). This product (2.14g) was dissolved in acetone

(20mL), followed by the addition of sodium iodide (2.55g) and refluxing for 10 hours. Subsequently, water was added and the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1) to give the desired product as a colorless oil (1.47g).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.59-1.65(2H, m), 1.83-1.89(2H, m), 2.75(2H, t, J=7.8Hz), 3.31(2H, s), 4.19(1H, d, J=9.3Hz), 4.21(1H, d, J=9.3Hz), 5.02(2H, s), 5.13(1H, br s), 6.88(1H, dd, J=7.8Hz, 2.0Hz), 6.94-7.00(2H, m), 7.11(1H, d, J=7.8Hz), 7.16(1H, dd, J=7.8Hz, 2.0Hz), 7.22-7.41(7H, m)

<Example 122>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-methylthiomethyl-2-oxazolidinone



The compound of Example 121 (1.47g) was dissolved in THF (30mL), followed by the addition of NaSMe (210mg) and stirring 2 hours at room temperature. Subsequently, water was added and

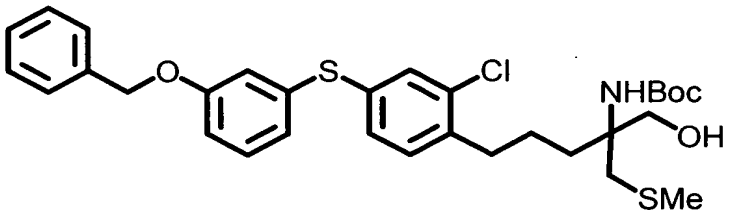
the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure to give the desired product as a colorless oil (1.27g).

FABMS: 514 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.62-1.77(4H, m), 2.17(3H, s), 2.68(1H, d, J=13.2Hz), 2.74(2H, t, J=7.3Hz), 2.78(1H, d, J=13.2Hz), 4.15(1H, d, J=9.0Hz), 4.20(1H, d, J=9.0Hz), 5.03(2H, s), 5.22(1H, br s), 6.87-6.90(1H, m), 6.93-6.97(2H, m), 7.10-7.17(2H, m), 7.22-7.41(7H, m)

<Example 123>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methylthiomethylpentane-1-ol



The compound of Example 122 (1.27g) was dissolved in acetonitrile (20mL), followed by the addition of Boc_2O (1.09g) and dimethylaminopyridine (100mg) and stirring at room temperature for 30min. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 4:1) to give N-Boc-

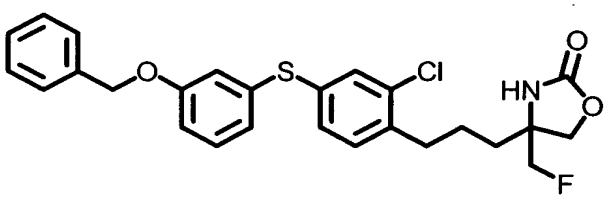
oxazolidinone product as a colorless oil (1.48g). This product was dissolved in methanol(20mL), which was followed by the addition of cesium carbonate (410mg) and stirring at room temperature overnight. Subsequently, the solvent was removed and the residue was dissolved in ethyl acetate. The solution was washed with hydrochloric acid and then water. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 2:1) to give the desired product as a colorless oil (1.28g).

FABMS: 588 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.51-1.66(3H, m), 1.82-1.85(1H, m), 2.15(3H, s), 2.69(2H, t, J=7.3Hz), 2.75(1H, d, J=13.4Hz), 2.90(1H, d, J=13.4Hz), 3.69-3.70(2H, m), 4.02(1H, br), 4.99(1H, br s), 5.02(2H, s), 6.86-6.94(3H, m), 7.12-7.17(2H, m), 7.21-7.41(7H, m)

<Example 124>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-fluoromethyl-2-oxazolidinone



To an acetonitrile solution (10mL) of the compound of Example 120 (600mg), triethylamine (0.52mL) and

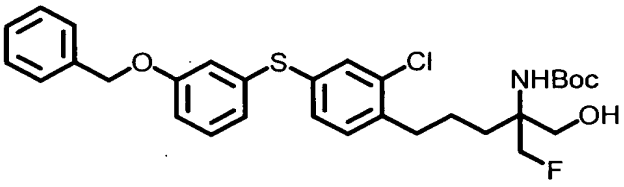
methanesulfonyl chloride (0.19mL) were added while the solution was chilled in an ice bath. The mixture was stirred for 10min. Subsequently, water was added and the solution was separated into an organic phase and an aqueous phase using ethyl acetate and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, was concentrated, and was dried in a vacuum pump. This gave 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-methanesulfonyloxymethyl-2-oxazolidinone as a yellow oil. The resulting mesylated product was dissolved in THF (6mL), followed by the addition of a THF solution (6.20mL) of 1mol/L tetrabutylammonium fluoride and refluxing for 1 hour. Subsequently, the reaction mixture was allowed to cool to room temperature and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1) to give the desired product as a colorless amorphous (300mg).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.67-1.70 (4H, m), 2.75 (2H, t, J= 7.03), 4.12 (1H, d, J=9.2Hz), 4.19 (1H, d, J=9.2Hz), 4.26 (1H, s), 4.38 (1H, s), 5.02 (2H, s), 5.13 (1H, br), 6.88-6.90 (1H, m), 6.91-6.97 (2H, m), 7.09-7.14 (2H, m), 7.22-7.26 (1H, m), 7.32-7.39 (6H, m)

<Example 125>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-

butoxycarbonylamino-2-fluoromethylpentane-1-ol

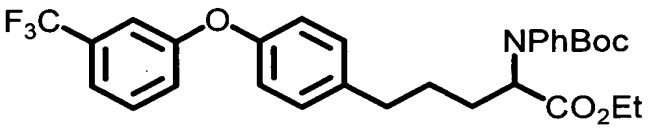


Using the compound of Example 124, the reaction was carried out in the same manner as in Example 123 to give the desired product as a colorless oil.

^{1}NMR(400MHz, $CDCl_3$) δ 1.64-1.77 (4H, m), 1.47 (9H, s), 2.71 (2H, t, J =7.34), 3.68-3.76 (3H, m), 4.43 (1H, dd, J=9.2Hz, J=20.2Hz), 4.55 (1H, dd, J=9.2Hz, J=20.2Hz), 4.81 (1H, br), 5.02 (2H, s), 6.86-6.89 (1H, m), 6.92-6.94 (2H, m), 7.11-7.16 (2H, m), 7.21-7.25 (1H, m), 7.30-7.40 (6H, m).

<Example 126>

Ethyl N-phenyl-2-t-butoxycarbonylamino-5-[4-(3-trifluoromethylphenoxy)phenyl]pentanoate



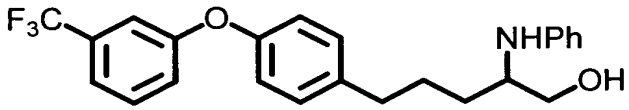
To a THF solution (10mL) of diethyl 2-phenylaminomalonate (510mg), Boc_2O (480mg) was added and the mixture was stirred at room temperature for 1 day. To the resulting reaction mixture, NaOtBu (190mg) and a THF solution (2mL) of the compound of Reference Example 134 (810mg) were added and the mixture was refluxed for 8 hours. Subsequently, the mixture was poured into ice water and the mixture was extracted with ethyl

acetate. The extract was then washed with a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 6:1) to give the desired product as a colorless oil (420mg).

FABMS: 558 ($[M+H]^+$)

<Example 127>

2-phenylamino-5-[4-(3-trifluoromethylphenoxy)phenyl]pentane-1-ol



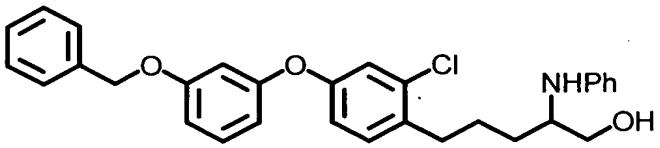
Using the compound of Example 126, the reaction was carried out in the same manner as in Example 39 to give the desired product as a colorless oil.

MS(EI): 415 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.56-1.78(4H, m),2.62(2H, t, J=7.8Hz), 3.51-3.56(2H, m), 3.73-3.77(1H,m), 6.66(2H,d,J=7.8Hz), 6.73(1H, t, J=7.8Hz), 6.91-6.95(2H, m), 7.11-7.21(6H, m), 7.31(1H, d, J=7.8Hz), 7.41(1H, t, J=7.8Hz)

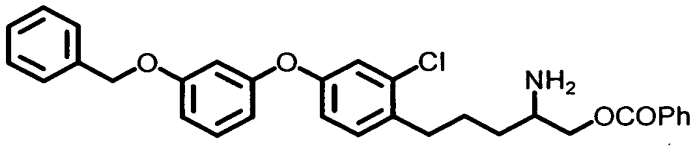
<Example 128>

5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-phenylaminopentane-1-ol



<Example 128-1>

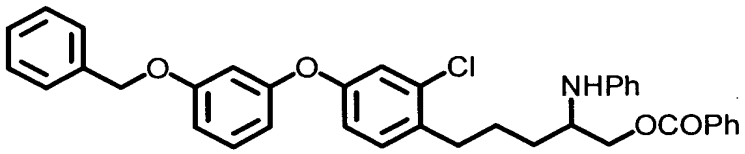
2-amino-1-benzoyloxy-5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]pentane



The compound of Example 75 (500mg) was dissolved in methylene chloride (10mL). To this solution, pyridine (0.2mL) and benzoylchloride (0.12mL) were added and the mixture was stirred at room temperature for 1 hour. Following addition of water, the reaction mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was dissolved in methanol (20mL). To this solution, ethyl acetate containing 3mol/L hydrochloric acid (10mL) was added and the mixture was stirred at room temperature for 1 hour. After concentration, a saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate to give the desired product as a colorless oil (670mg).

<Example 128-2>

1-benzoyloxy-5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-phenylaminopentane



The compound of Example 128-1 (670mg) was dissolved in methylene chloride (30mL). To this solution, $Ph_3Bi(OAc)_2$ (558mg) and copper acetate (10mg) were added and the mixture was stirred at room temperature for 1 day. Subsequently, the solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 4:1) to give the desired product as a colorless oil (560mg).

FABMS: 592 ($[M+H]^+$)

<Example 128-3>

5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-phenylaminopentane-1-ol

The compound of Example 128-2 (560mg) was dissolved in ethanol (10mL). To this solution, a 1mol/L aqueous solution of sodium hydroxide (5mL) was added and the mixture was stirred at room temperature for 1 hour. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed with a saturated aqueous solution of sodium

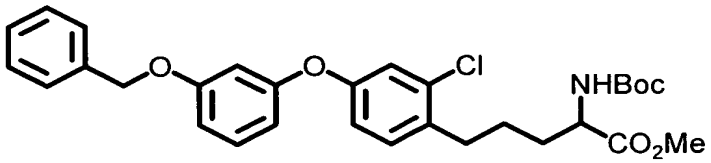
chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 2:1) to give the desired product as a colorless oil (290mg).

FABMS: 488 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.57-1.73(4H, m), 2.70(2H, t, J=7.3Hz), 3.53-3.56(2H, m), 3.74-3.79(1H, m), 5.02(2H, s), 6.57-6.75(6H, m), 6.82(1H, dd, J=8.3Hz, 2.4Hz), 6.99(1H, d, J=2.4Hz), 7.09(1H, d, J=8.3Hz), 7.17(2H, dd, J=8.3Hz, 7.3Hz), 7.23(1H, t, J=8.3Hz), 7.30-7.42(5H, m)

<Example 129>

Methyl 5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-t-butoxycarbonylaminopentanoate



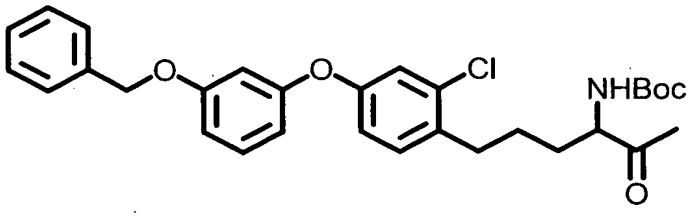
5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-t-butoxycarbonylaminopentane-1-ol (the compound of Example 75, 4.20g) was dissolved in DMF (50mL). To this solution, pyridinium dichromate (9.26g) was added and the mixture was stirred at room temperature for 17 hours. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated

aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was dissolved in DMF (50mL), followed by the addition of potassium carbonate (2.00g) and methyl iodide (2mL) and stirring at room temperature overnight. Subsequently, water was added and the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate=4:1) to give the desired methyl ester product as a colorless oil (2.67g).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 1.65-1.88(4H, m), 2.69-2.71(2H, m), 3.74(3H, s), 4.34(1H, br), 5.00(1H, br), 5.03(2H, s), 6.60(1H, ddd, J=8.0Hz, 2.2Hz, 0.7Hz), 6.63(1H, t, J=2.4Hz), 6.75(1H, ddd, J=8.3Hz, 2.4Hz, 0.7Hz), 6.84(1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.13(1H, d, J=8.3Hz), 7.24(1H, t, J=8.0Hz), 7.30-7.43(5H, m)

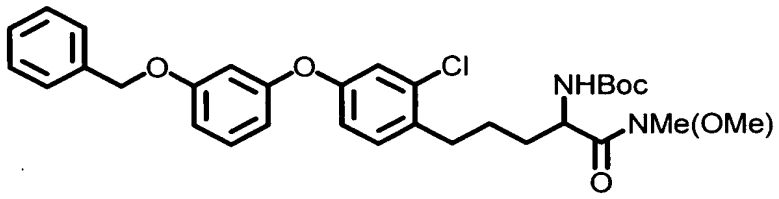
<Example 130>

6-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-3- t-butoxycarbonylaminohexane-2-one



<Example 130-1>

N-methoxy-N-methyl-5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-t-butoxycarbonylaminopentane amide



The compound of Example 129 (2.67g) was dissolved in ethanol (100mL). To this solution, a 1mol/L aqueous solution of sodium hydroxide (20mL) was added and the mixture was stirred at room temperature for 1 hour. Subsequently, hydrochloric acid was added to make the solution acidic and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure to give the carboxylic acid product as a colorless oil (2.60g). The resulting carboxylic acid (2.40g) was dissolved in methylene chloride (50mL), followed by the addition of MeONHMe.HCl (780mg), triethylamine (1.1mL), and WSC (1.53g) and then stirring at room temperature for 8 hours. Subsequently, water was added and the mixture was extracted

with ethyl acetate. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 2:1) to give the desired amide as a colorless oil (1.12g).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.52-1.78(4H, m), 2.67-2.77(2H, m), 3.20(3H, s), 3.76(3H, s), 4.73(1H, br), 5.03(2H, s), 5.17(1H, br), 6.59(1H, dd, J=8.3Hz, 2.4Hz), 6.62(1H, t, J=2.4Hz), 6.74(1H, dd, J=8.3Hz, 2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.99(1H, d, J=2.4Hz), 7.14(1H, d, J=8.3Hz), 7.23(1H, t, J=8.3Hz), 7.28-7.52(5H, m)

<Example 130-2>

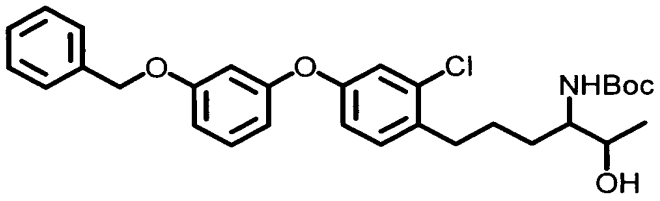
6-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-3-t-butoxycarbonylaminohexane-2-one

The compound of Example 130-1 (570mg) was dissolved in THF (15mL). To this solution, a THF solution (2mL) of 3mol/L MeMgBr was added at 0°C and the mixture was stirred for 3 hours. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 3:1) to give the desired product as a colorless oil (200mg).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 1.53-1.70(3H, m), 1.93(1H, br), 2.19(3H, s), 2.67-2.75(2H, m), 4.35(1H, br), 5.03(2H, s), 5.19(1H, d, J=7.0Hz), 6.59(1H, ddd, J=8.3Hz, 2.4Hz, 0.7Hz), 6.62(1H, t, J=2.4Hz), 6.75(1H, ddd, J=8.3Hz, 2.4Hz, 0.7Hz), 6.84(1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.13(1H, d, J=8.3Hz), 7.24(1H, t, J=8.0Hz), 7.31-7.43(5H, m)

<Example 131>

6-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-3-t-butoxycarbonylaminohexane-2-ol



$LiBH_4$ (50mg) was added to the compound of Example 130 in a mixture of THF (15mL) and ethanol (3mL). The mixture was stirred at room temperature for 1 hour. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1) to give the desired product as a colorless oil (320mg).

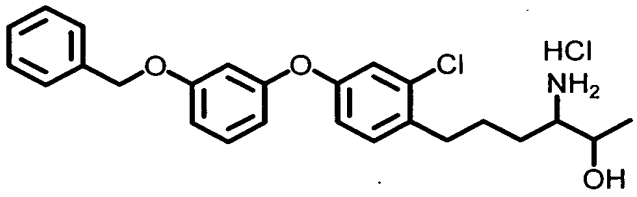
FABMS: 526 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.13(3H, d, J=6.3Hz), 1.44(9H, s),

1.64-1.72(4H, m), 2.64-2.76(2H, m), 3.67(1H, br), 3.86(1H, br), 4.55(1H, d, J=8.3Hz), 5.03(2H, s), 5.19(1H, d, J=7.0Hz), 6.60(1H, dd, J=8.3Hz, 2.2Hz), 6.62(1H, t, J=2.2Hz), 6.75(1H, dd, J=8.3Hz, 2.2Hz), 6.84(1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.14(1H, d, J=8.3Hz), 7.24(1H, t, J=8.0Hz), 7.29-7.42(5H, m)

<Example 132>

3-amino-6-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]hexane-2-ol hydrochloride



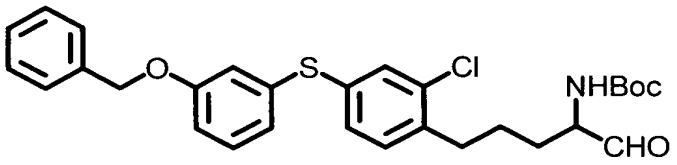
The compound of Example 131 was reacted in the same manner as in Example 76 to give the desired product as a brown amorphous.

FABMS: 426 ($[M+H]^+$)

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.03-1.06(3H, m), 1.65-1.71(4H, m), 2.67(2H, br), 3.03(1H, br), 3.84-3.87(1H, m), 5.08(2H, s), 6.56(1H, dd, J=8.3Hz, 2.4Hz), 6.66(1H, t, J=2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.94(1H, dd, J=8.3Hz, 2.4Hz), 7.06(1H, d, J=2.4Hz), 7.14-7.43(7H, m), 7.82(3H, br)

<Example 133>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylaminopentanal

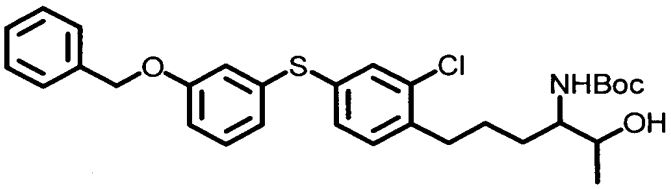


At -78°C, a mixture of DMSO (1.7mL) and methylene chloride (10mL) was added to an oxalyl chloride solution (1.0mL) of methylene chloride (20mL). To this mixture, a methylene chloride solution (20mL) of the compound of Example 65 (5.59g) was added dropwise. After 15min, triethylamine (7.2mL) was added and the mixture was stirred at room temperature for 2 hours. Following addition of water, the mixture was extracted with ethyl acetate and the organic phase was dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 3:1) to give the desired product as a pale yellow oil (4.75g).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 1.60-1.74(3H, m), 1.96(1H, br), 2.72-2.77(2H, m), 4.28(1H, br), 5.02(2H, s), 6.87-6.95(3H, m), 7.10-7.16(2H, m), 7.23(1H, t, J=7.8Hz), 7.28-7.52(6H, m), 9.58(1H, s)

<Example 134>

6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3- t-butoxycarbonylaminohexane-2-ol



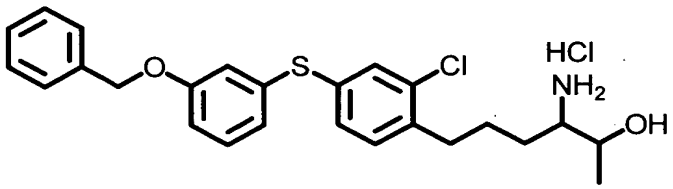
In the same manner as in Example 131, the compound of Example 133 was used to give the desired product as a colorless oil.

FABMS: 542 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.12(1H, d, J=6.1Hz), 1.19(2H, d, J=6.1Hz), 1.44(9H, s), 1.64-1.70(4H, m), 2.68-2.75(2H, m), 3.49-3.85(2H, m), 4.54-4.62(1H, br), 5.02(2H, s), 6.86-6.88(1H, m), 6.91-6.94(2H, m), 7.14-7.16(2H, m), 7.22(1H, t, J=7.8Hz), 7.26-7.40(6H, m)

<Example 135>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]hexane-2-ol hydrochloride



In the same manner as in Example 76, the compound of Example 134 was used to give the desired product as a pale brown oil.

FABMS: 442 ($[M+H]^+$)

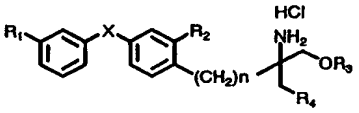
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.03(1H, d, J=6.1Hz), 1.10(2H, d, J=6.1Hz), 1.52-1.65(4H, m), 2.68(2H, br s), 2.86-3.02(1H, m),

3.65-3.84(1H, m), 5.08(2H, s), 5.26-5.36(1H, m), 6.89(1H, d, J=7.8Hz), 6.94-7.00(2H, m), 7.23(1H, dd, J=7.8Hz, 1.8Hz), 7.29-7.41(8H, m), 7.78-7.82(3H, br)

<Examples 136 through 145>

In the same manner as in Example 76, the compounds of 112 through 119, 123 and 125 were used to synthesize the compounds shown in Table 10 below.

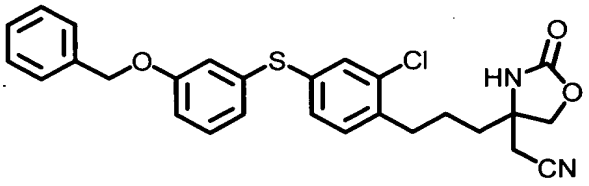
Table 10



Examples	R1	R2	R3	R4	X	n	Characteristics	Yield (%)	FABMS [M+H]+
136	$PhCH_2O$	Cl	H	OMe	O	3	Colorless oil	100	456
137	$PhCH_2O$	Cl	Me	OMe	O	3	Colorless oil	100	470
138	CF_3	H	H	OMe	O	3	Colorless oil	92	384
139	CF_3	H	Me	OMe	O	3	Colorless oil	98	398
140	$PhCH_2O$	Cl	H	SMe	S	3	Colorless amorphous	100	488
141	$PhCH_2O$	Cl	H	OMe	S	2	Colorless amorphous	100	458
142	$PhCH_2O$	Cl	Me	OMe	S	2	Colorless amorphous	92	472
143	$PhCH_2O$	Cl	H	OMe	S	3	Colorless amorphous	87	472
144	$PhCH_2O$	Cl	Me	OMe	S	3	Colorless amorphous	90	486
145	$PhCH_2O$	Cl	H	CH_2F	S	3	Colorless amorphous	97	460

<Example 146>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-cyanomethyl-2-oxazolidinone



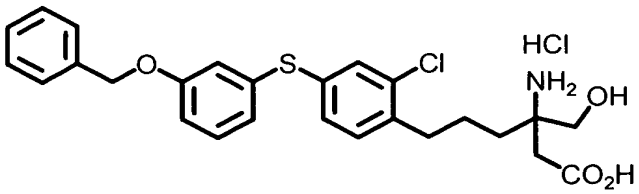
To an ice-chilled acetonitrile solution (8mL) of the compound of Example 120 (610mg), triethylamine (0.35mL) and methanesulfonyl chloride (0.13mL) were added and the mixture

was stirred for 15min. Subsequently, water was added and the solution was separated into an organic phase and an aqueous phase using ethyl acetate and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, was concentrated, and was dried in a vacuum pump. This gave the mesylated product as a yellow oil. This product was dissolved in DMF (2.5mL), followed by the addition of potassium cyanide (246mg) and stirring at 70°C for 2 hours. Subsequently, the reaction mixture was allowed to cool to room temperature and was separated into an organic phase and an aqueous phase using a saturated aqueous solution of sodium bicarbonate and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and was then concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1) to give the desired product as a colorless amorphous (574mg).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.63-1.72 (2H, m), 1.78-1.91 (2H, m), 2.67 (2H, s), 2.73 (2H, t, J=7.3Hz), 4.21 (2H, s), 5.03 (2H, s), 5.33 (1H, br), 6.89-6.91 (1H, m), 6.95-6.97 (2H, m), 7.09-7.16 (2H, m), 7.22-7.25 (1H, m), 7.27-7.42(6H, m)

<Example 147>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylhexanoate hydrochloride

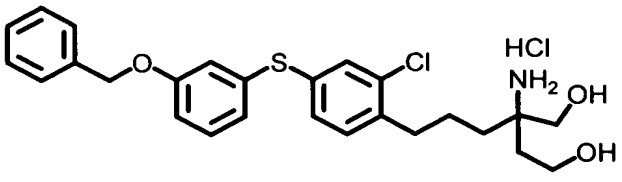


To the compound of Example 146 (196mg), a 3mol/L aqueous solution of sodium hydroxide (5mL) and ethanol (0.5mL) were added and the mixture was refluxed for 8 hours. While the mixture was stirred in an ice bath, 4mol/L hydrochloric acid was added to adjust the pH of the mixture to 2 to 1. Using ethyl acetate and water, the mixture was separated into an organic phase and an aqueous phase. The organic layer was dried over anhydrous sodium sulfate, was concentrated, and was dried in a vacuum pump to give the desired product as a pale white solid (201mg).

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.58-1.71 (4H, m), 2.55 (2H, s), 2.65 (2H, t, J= 7.3Hz), 3.46 (1H, d, J=11.0Hz), 3.52 (1H, d, J=11.0Hz), 5.10 (2H s), 5.50 (1H, br), 6.90-6.91 (1H, m), 6.96-7.02 (2H, m), 7.22-7.25 (1H, m), 7.30-7.42 (8H, m), 7.86 (3H, br)

<Example 148>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylhexanol hydrochloride



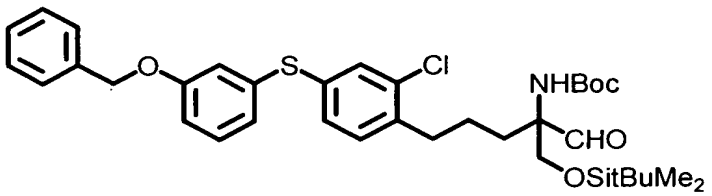
To a dichloromethane solution (8mL) of the compound of Example 147 (569mg), triethylamine (303μL) was added and the mixture was stirred for 5min. While the mixture was chilled in an ice bath, Boc_2O (358 mg) was added and the mixture was stirred for 1 hour. 4N hydrochloric acid was added to adjust the pH of the mixture to 2 to 1. This was followed by the addition of ethyl acetate and a saturated aqueous solution of sodium chloride to separate the mixture into an organic phase and an aqueous phase. The organic layer was dried over anhydrous sodium sulfate, was concentrated, and was dried in a vacuum pump to give a yellow oil. This product was dissolved in DMF (8 mL). To this solution, potassium carbonate (451mg) and methyl iodide (135mL) were added and the mixture was stirred at room temperature for 2 hours. The mixture was then extracted with ethyl acetate and the organic layer was dried over anhydrous sodium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 3:1). While chilled in an ice bath, the resultant oil was dissolved in THF (10mL). To this solution, lithium tetrahydroborate (40.4mg) and ethanol (1.5mL) were added and the mixture was stirred in an ice bath for 10min and at room temperature for the subsequent 1 hour. Following addition of water, 4N hydrochloric acid was added to adjust the pH of the mixture to 2 to 1. Ethyl acetate and water were added to separate the mixture into an organic phase

and an aqueous phase. The organic layer was dried over anhydrous sodium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:1). Methanol hydrochloride (4mL) was added to the resultant oil and the mixture was left overnight at room temperature. Subsequently, the solvent was removed to give the desired product as a colorless amorphous (70.0mg).

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.60 (4H, m), 1.68 (2H, t, J =6.7Hz), 2.67 (2H, m), 3.41-3.43 (2H, m), 3.50 (2H, t, J =6.7Hz), 5.10 (2H s), 5.40-5.42 (1H, br), 6.89-6.91 (1H, m), 6.96-7.01 (2H, m), 7.23-7.26 (1H, m), 7.30-7.43 (8H, m), 7.66 (3H, br).
HRMS: 472.1709 (-0.5mmu)

<Example 149>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-t-butyldimethylsiloxymethylpentanal



2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-2-t-butoxycarbonylamino-1,3-propanediol (19.3g) was dissolved in DMF (200mL). To this solution, triethylamine (12.5mL) and t-$BuMe_2SiCl$ (5.12g) were added and the mixture was stirred at room temperature for 8 hours. Following addition of ice water,

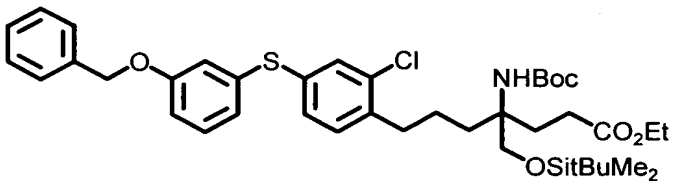
the mixture was extracted with ethyl acetate and the extract was washed with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10:1) to obtain a monosilyl product (18.0g) as a colorless oil. This monosilyl product was reacted in the same manner as in Example 133 to give the desired product as a pale yellow oil.

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.02(6H, s), 0.84(9H, s), 1.42(9H, s), 1.55-1.60(2H, m), 1.72-1.78(1H, m), 2.09-2.13(1H, m), 2.67(2H, t, J=7.9Hz), 3.85(1H, d, J=9.8Hz), 4.02(1H, d, J=9.8Hz), 5.02(2H, s), 5.31(1H, br s), 6.86-6.89(1H, m), 6.91-6.95(2H, m), 7.08(1H, d, J=7.9Hz), 7.13(1H, dd, J=7.9Hz, 1.8Hz), 7.23(1H, t, J=7.9Hz), 7.30-7.41(6H, m), 9.38(1H, s)

FABMS: 670 ($[M+H]^+$)

<Example 150>

Ethyl 7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-t-butoxycarbonylamino-4-t-butyldimethylsiloxymethylheptanoate



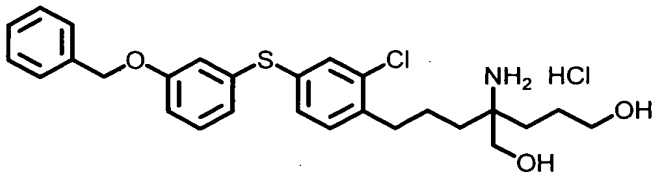
To an ice-chilled THF solution (8mL) of diethylphosphonoethyl acetate (246μL), sodium hydride (60%)

(50.0mg) was added and the mixture was stirred for 15min. A THF solution (7mL) of the compound of Example 149 (690mg) was then added and the mixture was stirred for 20min. Using ethyl acetate and water, the reaction mixture was separated into an organic phase and an aqueous phase. The organic layer was dried over anhydrous sodium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 4:1) to obtain an unsaturated ester as a colorless oil (733mg). The resultant compound was dissolved in ethyl acetate (8mL) and 10% palladium carbon (440mg) was added to the solution. The reaction mixture was then stirred for 4 days under hydrogen atmosphere. Subsequently, palladium carbon was removed by filtration through Celite. The filtrate was concentrated and was dried to give the desired product as a colorless oil (700mg).

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.3 (6H, s), 0.87 (9H, s), 1.24 (3H, t, J=7.3Hz), 1.41 (9H, s), 1.40-1.58 (2H, m), 1.69-1.74 (2H, m), 1.95-1.99 (2H, m), 2.29 (2H, t, J=8.0Hz), 2.67 (2H, t, J=7.3Hz), 3.55 (2H, s), 4.12 (2H, q, J=7.3Hz), 4.51 (1H, br), 5.02 (2H, s), 6.85-6.88(1H, m), 6.91-6.95 (2H, m), 7.10-7.18 (2H, m), 7.20-7.24 (1H, m), 7.30-7.40 (6H, m).

<Example 151>

4-amino-7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-hydroxymethylheptanol hydrochloride



To an ice-chilled THF solution (40mL) of the compound of Example 150 (690mg), lithium tetrahydroborate (90.2mg) and ethanol (5 mL) were added and the mixture was stirred in an ice bath for 1 hour. Subsequently, the mixture was allowed to warm to room temperature and was left overnight. On the next day, lithium tetrahydroborate (90.2mg) was added twice and the mixture was stirred for 4 hours. Subsequently, water was added and the resulting crystal was removed by filtration. Using ethyl acetate and water, the filtrate was separated into an organic phase and an aqueous phase. The organic layer was dried over anhydrous sodium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain a diol product as a colorless oil (552mg). While chilled in an ice bath, the resulting diol was dissolved in THF (9mL) and tetrabutylammonium fluoride (1mol/L-THF, sol.) (945µL) was added. The resulting mixture was then stirred for 30min and was left overnight. Subsequently, the reaction mixture was concentrated and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1:3) to obtain a colorless oil. Methanol hydrochloride (10mL) was then added to this product and the mixture was left overnight. The

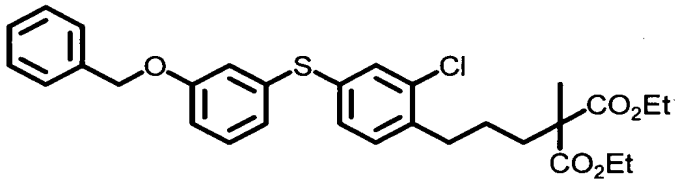
solvent was removed and the residue was dried in a vacuum pump to give the desired product as a colorless solid (363mg).

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.62-1.82 (8H, m), 2.70 (2H, t, J=7.3Hz), 3.61-3.67 (4H, m), 4.05 (1H, br), 5.00 (2H, s), 5.30 (1H, br), 6.84-6.87 (1H, m), 6.87-6.94 (2H, m), 7.10-7.23 (3H, m), 7.28-7.39 (6H, m), 7.98 (3H, br).

HRMS: 486.1887 (+1.7mmu).

<Example 152>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylpentanoate



Sodium hydride (242mg) was dissolved in DMF (5mL). To this solution, diethylmethylmalonate (0.956mL) was added and the mixture was stirred for 30min. A DMF solution (5mL) of the compound of Reference Example 131 (2.50g) was then added and the mixture was stirred for 1 hour. Subsequently, the reaction mixture was diluted with water and was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous magnesium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 20:1 shifted to 10:1) to give the

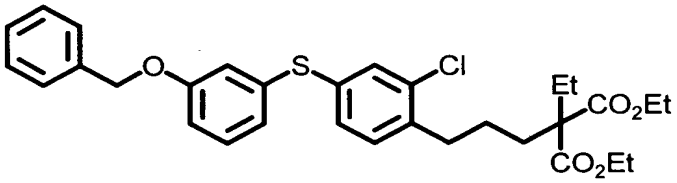
desired product as a yellow oil (2.74g).

MS(EI): 540 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.23(6H, t, J=7.3Hz), 1.40(3H, s), 1.52-1.60(2H, m), 1.91-1.95(2H, m), 2.70(2H, t, J=7.9Hz), 4.16(4H, q, J=7.3Hz), 5.02(2H, s), 6.86-6.94(3H, m), 7.11-7.14(2H, m), 7.20-7.24(1H, m) , 7.31-7.40(6H, m)

<Example 153>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylpentanoate



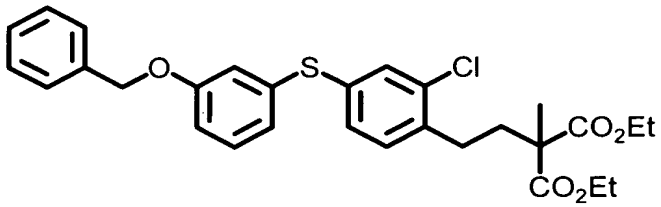
Using diethyl ethylmalonate, the reaction was carried out in the same manner as in Example 152 to give the desired product as a yellow oil.

MS(EI): 554 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.80(3H, t, J=7.3Hz), 1.22(6H, t, J=7.3Hz), 1.45-1.53(2H, m), 1.89-1.97(4H, m), 2.70(2H, t, J=7.3Hz), 4.16(4H, q, J=7.3Hz), 5.02(2H, s), 6.86-6.94(3H, m), 7.11-7.16(2H, m), 7.20-7.24(1H, m) , 7.31-7.40(6H, m)

<Example 154>

Ethyl 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylbutyrate



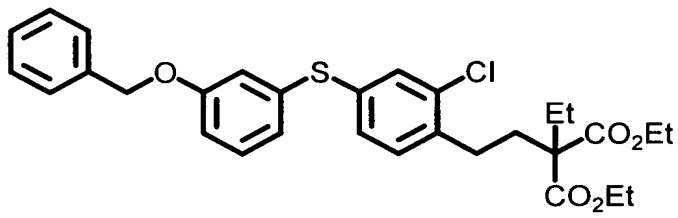
Using the compound of Reference Example 166, the reaction was carried out in the same manner as in Example 152 to give the desired product as a pale yellow oil.

MS(EI): 526 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.27(6H, t, J=7.3Hz), 1.52(3H, s), 2.10-2.14(2H, m), 2.65-2.69(2H, m), 4.20(4H, q, J=7.3Hz), 5.02(2H, s), 6.86-6.96(3H, m), 7.15(2H, s), 7.23(1H, t, J=8.0Hz), 7.31-7.41(6H, m)

<Example 155>

Ethyl 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylbutyrate



Using the compound of Reference Example 166, the reaction was carried out in the same manner as in Example 153 to give the desired product as a colorless oil.

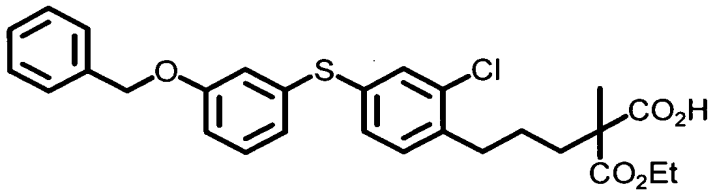
MS(EI): 540 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.82(3H, t, J=7.3Hz), 1.17(6H, t, J=7.3Hz), 1.93(2H, q, J=7.3Hz), 1.98-2.02(2H, m), 2.45-2.51(2H,

m), 4.13(4H, q, J=7.3Hz), 5.10(2H, s), 6.92-7.01(3H, m), 7.21(1H, dd, J=8.0Hz, 1.9Hz), 7.30-7.41(8H, m)

<Example 156>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylpentanoic acid



The compound of Example 152 (2.74g) was dissolved in ethanol (10mL). To this solution, potassium hydroxide (330mg) was added and the mixture was stirred at 50°C overnight. Subsequently, the reaction mixture was diluted with water. 2mol/L hydrochloric acid was then added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous magnesium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10:1 shifted to 2:1) to give the desired product as a yellow oil (2.38g).

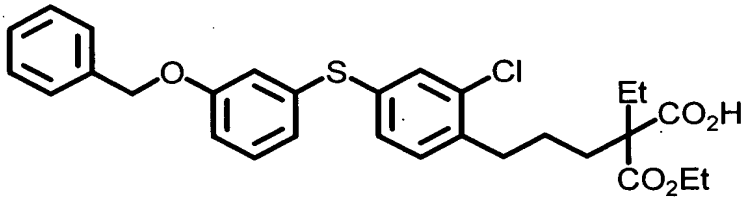
MS(EI): 512 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.26(3H, t, J=7.3Hz), 1.47(3H, s), 1.53-1.62(2H, m), 1.92-2.03(2H, m), 2.71(2H, t, J=7.9Hz), 4.22(2H, q, J=7.3Hz), 5.02(2H, s), 6.87-6.94(3H, m), 7.10-

7.14(2H, m), 7.21-7.25(1H, m) , 7.31-7.40(6H, m)

<Example 157>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylpentanoic acid



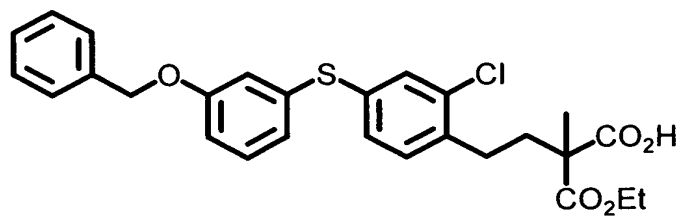
Using the compound of Example 153, the reaction was carried out in the same manner as in Example 156 to give the desired product as a yellow oil.

MS(EI): 526 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.84(3H, t, J=7.3Hz), 1.28(3H, t, J=7.3Hz), 1.42-1.59(2H, m), 1.85-1.95(2H, m), 2.00-2.13(2H, m), 2.66-2.70(2H, m), 4.23-4.31(2H, m), 5.02(2H, s), 6.86-6.94(3H, m), 7.08-7.15(2H, m), 7.21-7.25(1H, m) , 7.30-7.40(6H, m)

<Example 158>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylbutyric acid



Using the compound of Example 154, the reaction was

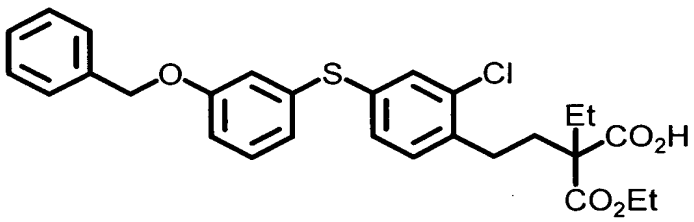
carried out in the same manner as in Example 156 to give the desired product as a pale yellow oil.

MS(EI): 499 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.30(3H, t, J=7.3Hz), 1.57(3H, s), 2.11-2.19(2H, m), 2.69(2H, t, J=8.5Hz), 4.24(2H, q, J=7.3Hz), 5.02(2H, s), 6.87-6.96(3H, m), 7.14(2H, s), 7.23(1H, t, J=8.0Hz), 7.31-7.40(6H, m)

<Example 159>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylbutyric acid



Using the compound of Example 155, the reaction was carried out in the same manner as in Example 156 to give the desired product as a pale yellow oil.

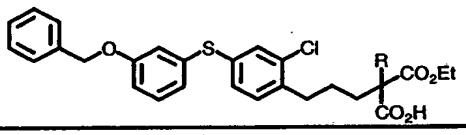
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.90(3H, t, J=7.3Hz), 1.33(3H, t, J=7.3Hz), 1.94-1.99(1H, m), 2.05-2.12(1H, m), 2.19-2.24(2H, m), 2.59-2.64(2H, m), 4.20-4.31(2H, m), 5.02(2H, s), 6.87-6.94(3H, m), 7.09-7.14(2H, m), 7.23(1H, t, J=8.0Hz), 7.29-7.40(6H, m)

<Examples 160 through 162>

Diethylpropyl malonate, diethylbutyl malonate or

dimethylallyl malonate was reacted in the same manner as in Example 152, which was followed by hydrolysis as described in Example 156 to synthesize the respective compounds shown in Table 11 below.

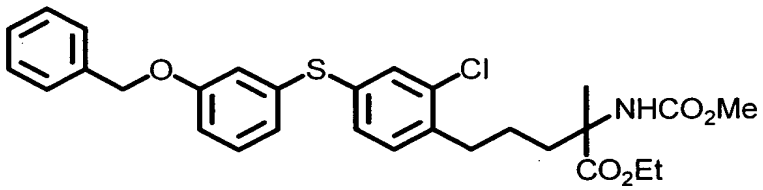
Table 11



Examples	R	Characteristics	MS(EI) M^+
160	Pr	Yellow oil	540
161	Bu	Yellow oil	554
162	$-CH_2CH=CH$	Yellow oil	—

<Example 163>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-methylpentanoate



The compound of Example 156 (2.38g) was dissolved in benzene (20mL). To this solution, triethylamine (0.711mL) and DPPA (1.10mL) were added and the mixture was stirred at room temperature for 10min, was refluxed, and was further stirred for 1 hour and 30min. Methanol (3.76mL) was added over a 30 minute-time period and the mixture was stirred overnight. Subsequently, the reaction mixture was diluted with water and was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, and was then dried over anhydrous magnesium sulfate and was

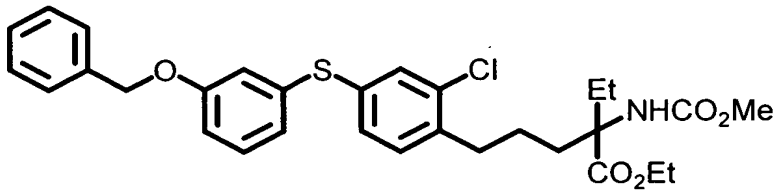
concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 20:1 shifted to 5:1) to give the desired product as a yellow oil (2.04g).

MS(EI): 541 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.24(3H, t, J=7.3Hz), 1.36-1.40(1H, m), 1.54(3H, s), 1.56-1.65(1H, m), 1.80-1.87(1H, m), 2.28(1H, m), 2.65-2.69(2H, m), 3.63(3H, s), 4.15-4.22(2H, m), 5.02(2H, s), 5.61(1H, br s), 6.86-6.94(3H, m), 7.09-7.15(2H, m), 7.20-7.24(1H, m), 7.31-7.40(6H, m)

<Example 164>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminopentanoate



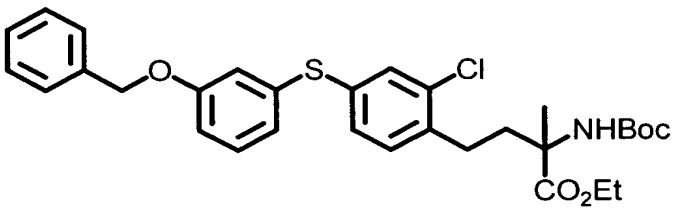
Using the compound of Example 157, the reaction was carried out in the same manner as in Example 163 to give the desired product as a yellow oil.

MS(EI): 555 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.74(3H, t, J=7.3Hz), 1.24(3H, t, J=7.3Hz), 1.28-1.32(1H, m), 1.57-1.58(1H, m), 1.70-1.84(2H, m), 2.34-2.44(2H, m), 2.62-2.72(2H, m), 3.63(3H, s), 4.16-4.22(2H, m), 5.02(2H, s), 5.78(1H, br s), 6.86-6.94(3H, m), 7.08-7.15(2H, m), 7.20-7.24(1H, m) , 7.31-7.40(6H, m)

<Example 165>

Ethyl 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2--t-butoxycarbonylamino-2-methylbutyrate



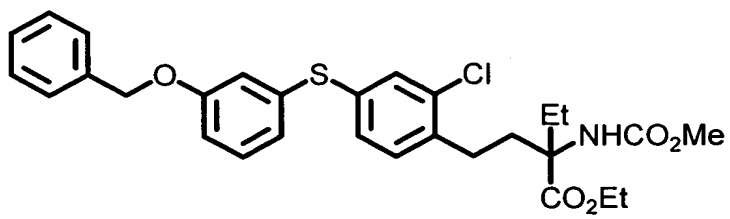
Using t-butanol in place of methanol, the compound of Example 158 was reacted in the same manner as in Example 163 to give the desired product as a pale yellow oil.

MS(FAB+): 569([M+H]$^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.29(3H, t, J=7.3Hz), 1.46(9H, s), 1.58(3H, s), 2.10(1H, td, J=13.0Hz, 4.9Hz), 2.41(1H, br), 2.53(1H, td, J=13.0Hz, 4.9Hz), 2.67(1H, td, J=13.0Hz, 4.9Hz), 4.19(2H, q, J=7.3), 5.02(2H, s), 5.46(1H, br s), 6.86-6.94(3H, m), 7.08-7.15(2H, m), 7.23(1H, t, J=8.0Hz), 7.30-7.40(6H, m)

<Example 166>

Ethyl 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminobutyrate



Using the compound of Example 159, the reaction was carried out in the same manner as in Example 163 to give the desired product as a pale yellow oil.

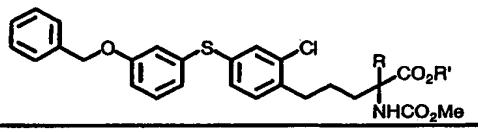
MS(EI): 541 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.77(3H, t, J=7.3Hz), 1.30(3H, t, J=7.3Hz), 1.75-1.80(1H, m), 2.05-2.15(1H, m), 2.36-2.49(2H, m), 2.59-2.68(2H, m), 3.66(3H, s), 4.11-4.27(2H, m), 5.02(2H, s), 5.87(1H, br), 6.86-6.93(3H, m), 7.08-7.14(2H, m), 7.22(1H, t, J=8.0Hz), 7.30-7.40(6H, m)

<Examples 167 through 169>

Using the compounds shown in Table 11, the reaction was carried out in the same manner as in Example 163 to give the respective compounds shown in Table 12 below.

Table 12

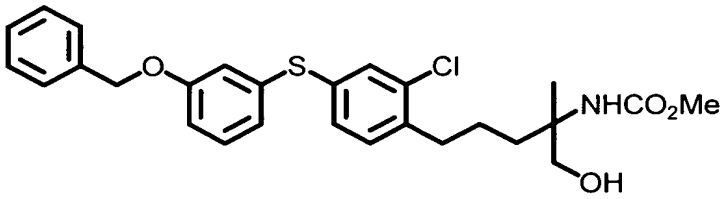


Examples	R	R'	Characteristics	MS(EI) M^+
167	Pr	Et	Colorless oil	569
168	Bu	Et	Colorless oil	—
169	$-CH_2CH=CH$	Me	Yellow oil	554*

* FABMS

<Example 169>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-methylpentane-1-ol



Using the compound of Example 163, the reaction was carried out in the same manner as in Example 39 to give the desired product as a colorless oil.

MS(EI): 499 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18(3H, s), 1.57-1.84(4H, m), 2.71(2H, t, J=7.3Hz), 3.59-3.69(3H, m), 3.63(3H, s), 4.71(1H, br s), 5.02(2H, s), 6.86-6.94(3H, m), 7.13-7.17(2H, m), 7.21-7.25(1H, m) , 7.30-7.41(6H, m)

<Examples 170 and 171>

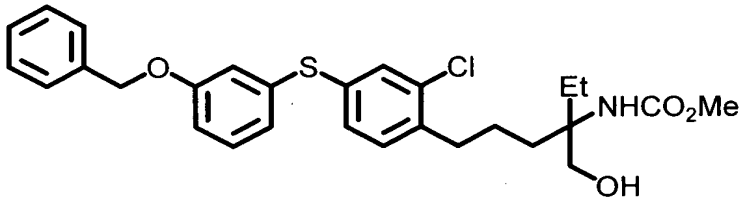
(+)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-methylpentane-1-ol and (-)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-methylpentane-1-ol

The compound of Example 169 was optically resolved by HPLC (Chiralcel OD, hexane: isopropanol = 70:30, wavelength = UV 254nm, flow rate = 3mL/min).

A compound with an optical rotation of $[\alpha]^{24.0}_D$ +15□ (C = 1.0, chloroform) and a compound with an optical rotation of $[\alpha]^{24.7}_D$ -12°(C = 1.0, chloroform) were obtained from the first elution fraction and the second elution fraction, respectively.

<Example 172>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminopentane-1-ol



Using the compound of Example 164, the reaction was carried out in the same manner as in Example 39 to give the desired product as a pale yellow oil.

MS(EI): 513 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.83(3H, t, J=7.3Hz), 1.51-1.73(6H, m), 2.70 (2H, t, J=7.3Hz), 3.63(3H, s), 3.65-3.70(3H, m), 4.63(1H, br s), 5.02(2H, s), 6.86-6.94(3H, m), 7.12-7.17(2H, m), 7.20-7.24(1H, m), 7.30-7.40(6H, m)

<Examples 173 and 174>

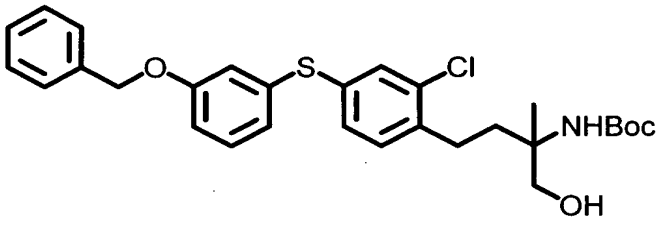
(+)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminopentane-1-ol and (-)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminopentane-1-ol

The compound of Example 172 was optically resolved by HPLC (Chiralcel OD, hexane: isopropanol = 60:40, wavelength = UV 254nm, flow rate = 3mL/min). A compound with an optical rotation of $[\alpha]^{25.6}_D$ +14°(C = 1.0, chloroform) and a compound with an optical rotation of $[\alpha]^{25.7}_D$ -15°(C = 1.0, chloroform)

were obtained from the first elution fraction and the second elution fraction, respectively.

<Example 175>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methylbutane-1-ol



Using the compound of Example 165, the reaction was carried out in the same manner as in Example 39 to give the desired product as a colorless oil.

MS(EI): 527 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.25(3H, s), 1.44(9H, s), 1.82(1H, td, J=13.0Hz, 4.9Hz), 2.06(1H, td, J=13.0Hz, 4.9Hz), 2.65-2.80(2H, m), 3.66-3.74(2H, m), 4.68(1H, br s), 6.86-6.94(3H, m), 7.15(2H, s), 7.23(1H, t, J=8.0Hz), 7.32-7.40(6H, m)

<Examples 176 and 177>

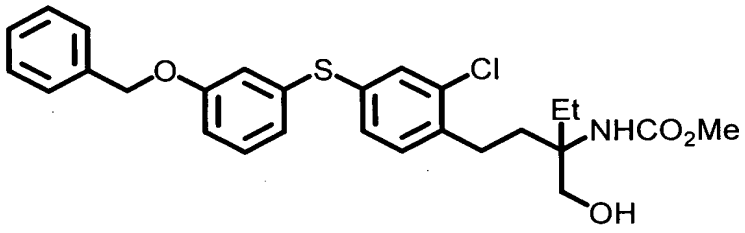
(+)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methylbutane-1-olおよび(-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methylbutane-1-ol

The compound of Example 175 was optically resolved by

HPLC (Chiralpak AD, hexane: ethanol = 85:15, wavelength = UV 254nm, flow rate = 3mL/min). A compound with an optical rotation of $[\alpha]^{25.3}_{D}$ +4.6°(C = 1.0, chloroform) and a compound with an optical rotation of $[\alpha]^{25.6}_{D}$ -2.2°(C = 1.0, chloroform) were obtained from the first elution fraction and the second elution fraction, respectively.

<Example 178>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylamino-butane-1-ol



Using the compound of Example 166, the reaction was carried out in the same manner as in Example 39 to give the desired product as a colorless oil.

MS(EI): 499 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.94(3H, t, J=7.3Hz), 1.69(2H, q, J=7.3Hz), 1.80-1.94(2H, m), 2.62-2.75(2H, m), 3.65(3H, s), 3.77(3H, m), 4.77(1H, br), 5.02(2H, s), 6.86-6.95(3H, m), 7.16(2H, s), 7.23(1H, t, J=8.0Hz), 7.32-7.41(6H, m)

<Examples 179 and 180>

(+)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-

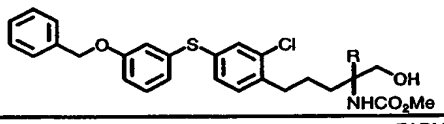
methoxycarbonylamino-butane-1-ol and (-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylamino-butane-1-ol

The compound of Example 178 was optically resolved under similar conditions to Examples 173 and 174. A compound with an optical rotation of $[\alpha]^{25.6}_{D}$ +11.1°(C = 1.0, chloroform) and a compound with an optical rotation of $[\alpha]^{26.1}_{D}$ -9.67°(C = 1.0, chloroform) were obtained from the first elution fraction and the second elution fraction, respectively.

<Examples 181 through 183>

Using the compounds shown in Table 12, the reaction was carried out in the same manner as in Example 39 to give the respective compounds shown in Table 13 below.

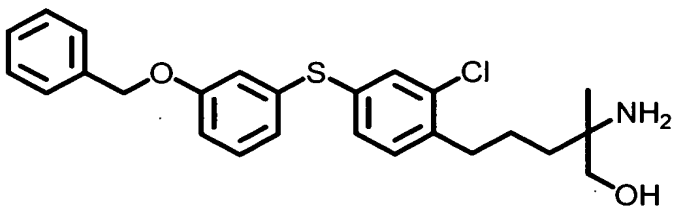
Table 13



Examples	R	Characteristics	FABMS $[M+H]^+$
181	Pr	Colorless oil	528
182	Bu	Colorless oil	—
183	$-CH_2CH=CH$	Colorless oil	526

<Example 184>

(±)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentane-1-ol



The compound of Example 169 (527mg) was dissolved in a mixed solvent composed of a 5mol/L aqueous solution of potassium hydroxide (2mL), tetrahydrofuran(2mL), and methanol(3mL). The mixture was refluxed and was then stirred for 4 days. Subsequently, the reaction mixture was diluted with water and was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride and was dried over anhydrous magnesium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (aminated silica gel, ethyl acetate: ethanol = 20:1) to give the desired product as a pale yellow oil (311mg).

MS(FAB+): 442($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04(3H, s), 1.37-1.67(4H, m), 2.70(2H, t, J=7.3Hz), 3.29(2H, q, J=9.2Hz), 5.02(2H, s), 6.86-6.94(3H, m), 7.12-7.17(2H, m), 7.21-7.25(1H, m) , 7.31-7.41(6H, m)

<Example 185>

(+)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentane-1-ol

Using the compound of Example 170, the reaction was carried out in the same manner as in Example 184 to give the desired product as a pale yellow oil.

Elemental analysis (%): $C_{25}H_{28}ClNO_2S \cdot 1/3H_2O$

	C	H	N
Calcd:	67.00	6.45	3.13
Found:	67.03	6.51	3.20

$[\alpha]^{25.2}_D$ +2.0° (C = 1.0, chloroform)

<Example 186>

(-)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentane-1-ol

Using the compound of Example 171, the reaction was carried out in the same manner as in Example 184 to give the desired product as a pale yellow oil.

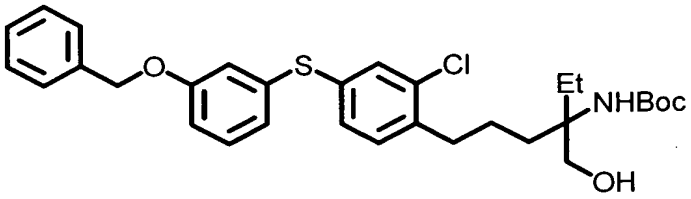
Elemental analysis (%): $C_{25}H_{28}ClNO_2S \cdot 1/4H_2O$

	C	H	N
Calcd:	67.23	6.44	3.14
Found:	67.19	6.44	3.15

$[\alpha]^{25.5}_D$ -2.6° (C = 1.0, chloroform)

<Example 187>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-butoxycarbonylamino-2-ethylpentane-1-ol



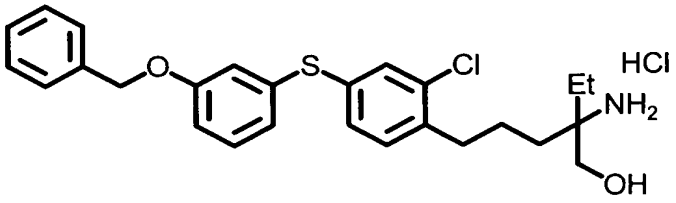
Using t-butanol in place of methanol, the compound of Example 157 was reacted in the same manner as in Example 163, followed by reduction to give the desired product as a colorless oil.

MS(EI): 555 ($[M]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.83(3H, t, J=7.3Hz), 1.42(9H, s), 1.55-1.72(6H, m), 2.70(2H, t, J=6.7Hz), 3.64-3.66(2H, m), 4.49(1H, br s), 5.02(2H, s), 6.82-6.95(3H, m), 7.12-7.17(2H, m), 7.20-7.25(1H, m) , 7.30-7.41(6H, m)

<Example 188>

(±)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylpentane-1-ol hydrochloride



Using the compound of Example 187, the reaction was carried out in the same manner as in Example 76 to give the desired product as a pale yellow amorphous.

MS(HR-FAB+): 456.1789

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.93(3H, t, J=7.3Hz), 1.65-1.75(6H, m), 2.69(2H, m), 3.66(2H, m), 4.21(1H, br s), 5.00(2H, s), 6.84-

6.94(3H, m), 7.12-7.23(3H, m), 7.29-7.39(6H, m)

<Example 189>

(+)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylpentane-1-ol

Using the compound of Example 173, the reaction was carried out in the same manner as in Example 184 to give the desired product as a pale yellow oil.

MS(HR-FAB+): 456.1753

Elemental analysis (%): $C_{26}H_{30}ClNO_2S \cdot 2/5H_2O$

	C	H	N
Calcd:	67.39	6.71	3.03
Found:	67.35	6.74	2.89

$[\alpha]^{25.2}_D$ +1.4°(C = 1.0, chloroform)

<Example 190>

(-)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylpentane-1-ol

Using the compound of Example 174, the reaction was carried out in the same manner as in Example 184 to give the desired product as a pale yellow oil.

MS(HR-FAB+): 456.1773

Elemental analysis (%): $C_{26}H_{30}ClNO_2S \cdot 2/5H_2O$

C H N

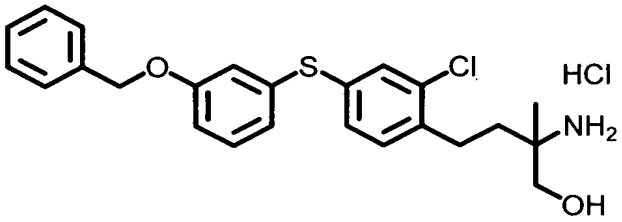
Calcd: 67.39 6.71 3.03

Found: 67.25 6.62 2.94

$[\alpha]^{25.5}_{D}$ -2.0° (C = 1.0, chloroform)

<Example 191>

(±)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutane-1-ol hydrochloride



Using the compound of Example 175, the reaction was carried out in the same manner as in Example 76 to give the desired product as a colorless powder.

MS(FAB+): 428([M+H]$^+$)

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.22(3H, s), 1.72-1.76(2H, m), 2.70(2H, t, J=8.5Hz), 3.39-3.43(1H, m), 3.47-3.50(1H, m), 5.10(2H, s), 5.54(1H, m), 6.90-7.02(3H, m), 7.24-7.42(9H, m), 7.77(3H, br).

MP = 150-153°C (iPr_2O)

<Example 192>

(+)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutane-1-ol hydrochloride

Using the compound of Example 176, the reaction was

carried out in the same manner as in Example 76 to give the desired product as a colorless powder.

MS(FAB+): 428([M+H]$^+$)

$[\alpha]^{24.9}_D$ +3.8°(C = 1.0, methanol)

MP = 157-159°C (iPr_2O)

<Example 193>

(-)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutane-1-ol hydrochloride

Using the compound of Example 177, the reaction was carried out in the same manner as in Example 76 to give the desired product as a colorless powder.

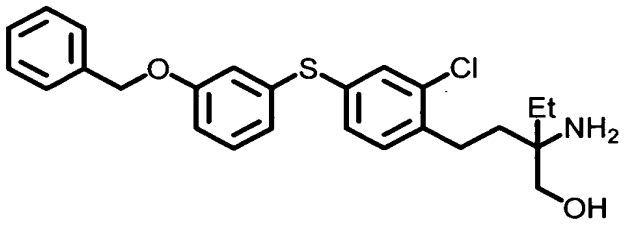
MS(FAB+): 428([M+H]$^+$)

$[\alpha]^{24.5}_D$ -4.3°(C = 1.0, methanol)

MP = 155-158°C (iPr_2O)

<Example 194>

(±)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylbutane-1-ol



Using the compound of Example 178, the reaction was carried out in the same manner as in Example 184 to give the

desired product as a pale yellow oil.

MS(FAB+): 442([M+H]$^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.93(3H, t, J=7.3Hz), 1.38-1.71(4H, m), 2.64-2.71(2H, m), 3.40(2H, s), 5.02(2H, s), 6.86-6.93(3H, m), 7.15(2H, s), 7.23(1H, t, J=8.0Hz), 7.31-7.40(6H, m)

<Example 195>

(+)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylbutane-1-ol

Using the compound of Example 180, the reaction was carried out in the same manner as in Example 184 to give the desired product as a colorless oil.

MS(FAB+): 442([M+H]$^+$)

$[\alpha]^{28.5}_D$ +2.7°(C = 1.0, chloroform)

<Example 196>

(-)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylbutane-1-ol

Using the compound of Example 179, the reaction was carried out in the same manner as in Example 184 to give the desired product as a colorless oil.

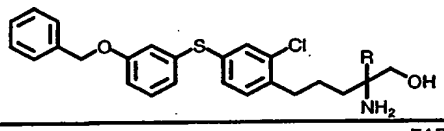
MS(FAB+): 442([M+H]$^+$)

$[\alpha]^{28.5}_D$ -3.3°(C = 1.0, chloroform)

<Examples 197 through 199>

The compounds shown in Table 13 were reacted in the same manner as in Example 184 to give the respective compounds shown in Table 14 below.

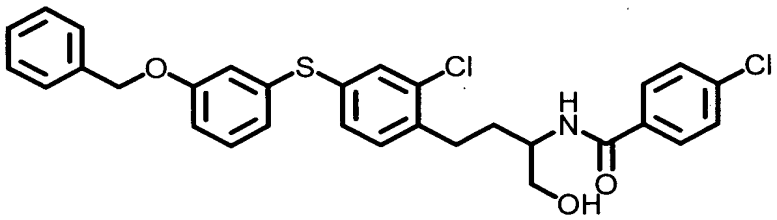
Table 14



Examples	R	Characteristics	FABMS $[M+H]^+$
197	Pr	Colorless oil	470
198	Bu	Colorless oil	484
199	$-CH_2CH=CH$	Colorless oil	468

<Example 200>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-(4-chlorobenzoyl)aminobutanol



A methylene chloride solution (30mL) containing the compound of Example 101 (900mg), p-chlorobenzoic acid (470mg), WSC (575mg), and triethylamine (0.84mL) was stirred at room temperature for 8 hours. Subsequently, water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water, diluted hydrochloric acid, water, a saturated aqueous solution of sodium bicarbonate, and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was purified on a

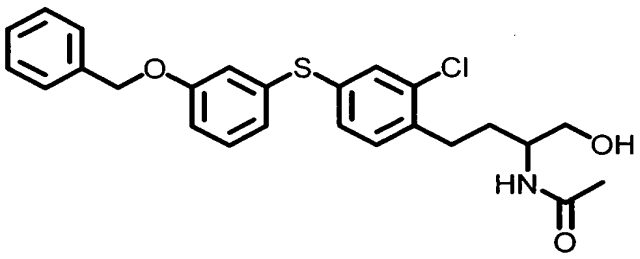
silica gel column chromatography (hexane: ethyl acetate = 1:1) to obtain the desired product as a colorless oil (800mg).

FABMS: 552([M+H]$^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.88-2.00(2H, m), 2.37(1H, br), 2.76-2.88(2H, m), 3.73-3.84(2H, m), 4.20-4.24(1H, m), 5.02(2H, s), 6.33(1H, d, J=8.0Hz), 6.88(1H, dd, J=7.3Hz, 1.8Hz), 6.90-6.94(2H, m), 7.13(1H, dd, J=8.0Hz, 1.8Hz), 7.17(1H, d, J=8.0Hz), 7.23(1H, d, J=8.0Hz), 7.30-7.39(6H, m), 7.41(2H, d, J=8.6Hz), 7.69(2H, d, J=8.6Hz)

<Example 201>

2-acetylamino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]butane-1-ol



To a methylene chloride solution (80mL) of the compound of Example 101 (5.55g), triethylamine (6.86ml), and acetyl chloride (3.50ml) were added while the mixture was chilled on an ice bath. The mixture was stirred for 4 hours, followed by the addition of water. The solvent was removed under reduced pressure and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous

sodium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (ethyl acetate) to obtain an N,O-diacetylated product as a colorless powder (4.21g). This compound (620mg) was dissolved in ethanol (2.00mL). To this solution, a 5N aqueous solution of potassium hydroxide (0.25mL) was added and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate and was concentrated. This gave the desired product as a colorless powder (552mg).

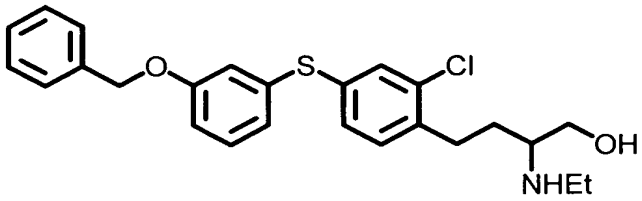
FABMS: 456($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.72-1.89(2H, m), 2.02(3H, s), 2.69-2.83(2H, m), 3.63(1H, dd, J=11.0Hz, 5.0Hz), 3.71(1H, dd, J=11.0Hz, 3.0Hz), 3.98-4.01(1H, m), 4.20-4.29(1H, m), 5.02(2H, s), 5.70(1H, d, J=7.9), 6.87-6.95(3H, m), 7.15(2H, s), 7.23(1H, t, J=8.4Hz), 7.31-7.41(6H, m)

MP = 78-81°C (EtOH).

<Example 202>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethylaminobutane-1-ol



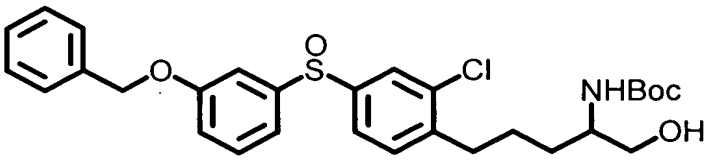
The N,O-diacetylated product (1.00g) obtained in Example 201 was dissolved in tetrahydrofuran (10mL). To this solution, lithium aluminum hydride (191mg) was added while the solution was chilled on an ice bath. The mixture was stirred for 2 hours. Subsequently, a 1mol/L aqueous solution of potassium hydroxide was added dropwise. This was followed by the addition of water to dilute the mixture. The mixture was then filtrated through Celite and the solvent was concentrated. The residue was purified on a silica gel column chromatography (aminated silica gel, ethyl acetate) to give the desired product as a colorless oil (210mg).

FABMS: 442($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.10(3H, t, J=7.3), 1.63-1.80(2H, m), 1.82(1H, br), 2.58-2.75(5H, m), 3.36(1H, dd, J=10.5Hz, 6.4Hz), 3.67(1H, dd, J=10.5Hz, 4.0Hz), 5.01(2H, s), 6.86-6.94(3H, m), 7.14(2H, s), 7.23(1H, t, J=7.3Hz), 7.31-7.40(6H, m)

<Example 203>

5-[4-(3-benzyloxyphenylsulfinyl)-2-chlorophenyl]-2-t-butoxycarbonylaminopentane-1-ol



To a methylene chloride solution (20mL) of the compound of Example 102, m-chlorobenzoic acid (588mg) was added while the mixture was chilled on an ice bath. The mixture was stirred for 30min. Following addition of a saturated aqueous solution of sodium bicarbonate, the solvent was removed under reduced pressure and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate and was concentrated. The residue was purified on a silica gel column chromatography (ethyl acetate: hexane = 2:1) to give the compound of Example 203 as a colorless amorphous (1.04g) and the compound of Example 204 as a colorless amorphous (180mg).

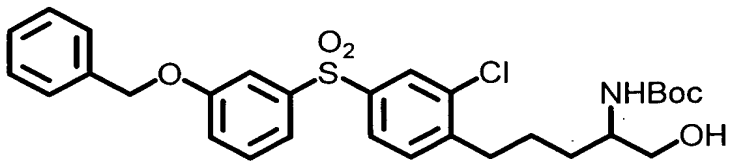
FABMS: 544($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.54-1.69(5H, m), 2.72-2.78(2H, m), 3.52-3.57(1H, m), 3.67(2H, d, J=8.5Hz), 4.63(1H, br), 5.10(1H, s), 7.05(1H, dd, J=8.6Hz, 2.0Hz), 7.19(1H, d, J=7.9Hz), 7.26-7.30(2H, m), 7.31-7.42(7H, m), 7.60(1H, d, J=1.2Hz)

<Example 204>

5-[4-(3-benzyloxyphenylsulfonyl)-2-chlorophenyl]-2-t-

butoxycarbonylaminopentane-1-ol



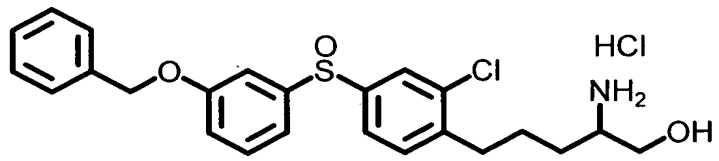
Colorless amorphous (See Example 203).

FABMS: 560([M+H]$^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.54-1.70(5H, m), 2.73-2.81(2H, m), 3.53-3.57(1H, m), 3.67(2H, d, J=8.5Hz), 4.62(1H, br), 5.10(1H, s), 7.15-7.18(1H, m), 7.32-7.44(7H, m), 7.52(2H, m, J=6.6Hz, 1.2Hz), 7.68(1H, dd, J=8.6Hz, 1.8Hz), 7.87(1H, d, J=1.9Hz)

<Example 205>

2-amino-5- [4-(3-benzyloxyphenylsulfinyl)-2-chlorophenyl]pentane-1-ol hydrochloride



Using the compound of Example 203, the reaction was carried out in the same manner as in Example 76 to give the desired product as a yellow powder.

FABMS: 454 ([M+H]$^+$)

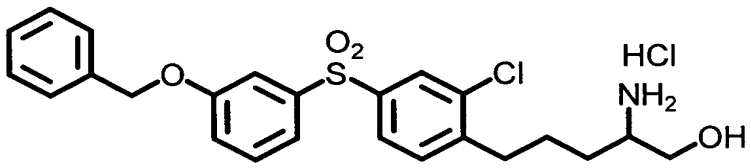
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.51-1.58(4H, m), 2.69(2H, t, J=7.3Hz), 3.06(1H, br), 3.38-3.44(1H, m), 3.53-3.58(1H, m), 5.15(2H, s), 5.26(1H, t, J=4.9Hz), 7.13(1H, dd, J=8.0Hz,

2.0Hz), 7.30-7.51(9H, m), 7.62(1H, dd, J=8.0Hz, 2.0Hz), 7.76(1H, d, J=2.0Hz), 7.84(3H, br)

MP = 114-116°C (CH_2Cl_2-iPr_2O)

<Example 206>

2-amino-5- [4-(3-benzyloxyphenylsulfonyl)-2-chlorophenyl]pentane-1-ol hydrochloride



Using the compound of Example 204, the reaction was carried out in the same manner as in Example 76 to give the desired product as a pale yellow powder.

FABMS: 460 ($[M+H]^+$)

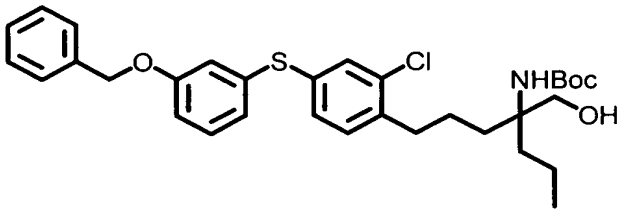
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.51-1.63(4H, m), 2.76(2H, t, J=7.3Hz), 3.08(1H, br), 3.40-3.43(1H, m), 3.56-3.58(1H, m), 5.21(2H, s), 5.27(1H, t, J=4.9Hz), 7.34-7.41(4H, m), 7.46(2H, d, J=6.7Hz), 7.55-7.61(4H, m), 7.80(3H, br), 7.88(1H, dd, J=8.6Hz, 1.8Hz), 8.00(1H, d, J=1.8Hz)

MP = 154-156°C (CH_2Cl_2-iPr_2O).

<Example 207 and 208>

(+)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-propyl-2-t-butoxycarbonylaminopentane-1-ol and (-)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-propyl-2-t-

butoxycarbonylaminopentane-1-ol



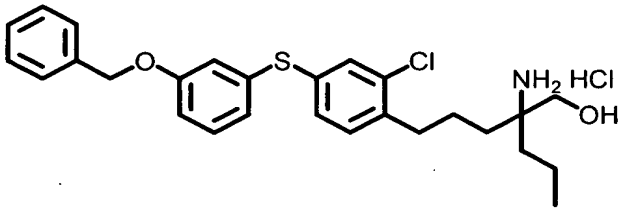
The compound of Example 197 was dissolved in acetonitrile. To this solution, Boc_2O was added and the reaction was allowed to proceed at room temperature. The solvent was removed and the residue was optically resolved by HPLC (Chiralpak OD-H, hexane: ethanol = 97:3, wavelength = UV 254nm, flow rate = 3mL/min). A colorless oil with an optical rotation of $[\alpha]^{25.1}_D$ -10.2°(C = 1.08, chloroform) and a colorless oil with an optical rotation of $[\alpha]^{22.9}_D$ +9.48°(C = 1.16, chloroform) were obtained from the first elution fraction and the second elution fraction, respectively.

FABMS: 570 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.90(3H, t, J=7.3Hz), 1.20-1.76(8H, m), 1.42(9H, s), 2.70(2H, t, J=7.3Hz), 3.63-3.66(2H, m), 4.51(1H, br), 5.02 (2H, s), 6.86-6.95(3H, m), 7.14-7.15(2H, m), 7.23(1H, d, J=7.8Hz), 7.33-7.41(6H, m)

<Example 209>

(+)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-propylpentane-1-ol



Using the compound of Example 208, the reaction was carried out in the same manner as in Example 76 to give the desired product as a colorless powder.

FABMS: 470 ($[M+H]^+$)

^{1}H-NMR(400MHz, DMSO-d_6) δ 0.83(3H, t, J=7.3Hz), 1.02-1.24(2H, m), 1.16-1.24(2H, m), 1.40-1.54(4H, m), 2.66(2H, br s), 3.37-3.38(2H, m), 5.08 (2H, s), 5.41-5.43(1H, m), 6.89(1H, d, J=7.3Hz), 6.95-7.00(2H, m), 7.23(1H, d, J=7.3Hz), 7.31-7.41(8H, m), 7.69-7.83(3H, br)

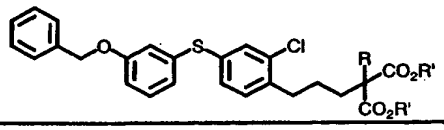
MP = 55-57°C

$[\alpha]^{23.4}_D$ +3.9°(C = 0.98, MeOH)

<Examples 210 and 211>

Using dimethylpropargylmalonate or diethylisobutylmalonate, the reaction was carried out in the same manner as in Example 152 to synthesize the respective compounds shown in Table 15 below.

Table 15

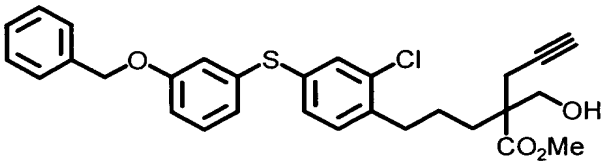


Examples	R	R'	Characteristics	MS(EI) M^+
210	$-CH_2CCH$	Me	Colorless oil	536
211	i-Bu	Et	Colorless oil	583*

* FABMS[M+H]$^+$

<Example 212>

Methyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethyl-2-propargylpentanoate

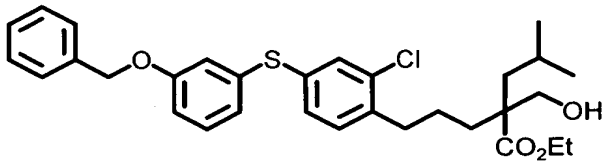


The compound of Example 210 (1.64g) was dissolved in THF (40mL). To this solution, $LiAl(OtBu)_3H$ (3.88g) was added while the solution was chilled on an ice bath. After stirring, the mixture was allowed to warm to room temperature and was further stirred for 2 days. The mixture was again ice-chilled, followed by the addition of diluted hydrochloric acid and filtration to remove the insoluble material. The mixture was then extracted with ethyl acetate and the extract was washed with a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate, and the solvent was removed and was concentrated. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 2:1) to give the desired product as a colorless oil (1.12g).

FABMS: 508 ($[M+H]^+$)

<Example 213>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-isobutyl-2-hydroxymethylpentanoate



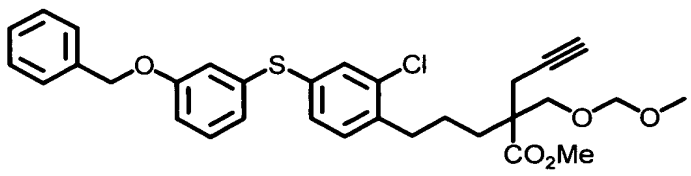
Using the compound of Example 211, the reaction was carried out in the same manner as in Example 212 to give the desired product as a colorless oil.

MS(EI): 540 $[M]^+$

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.85(3H, d, J=6.7Hz), 0.86(3H, d, J=6.7Hz), 1.26(3H, t, J=7.3Hz), 1.45-1.77(7H, m), 2.16(1H, t, J=6.7Hz), 2.68(2H, t, J=7.3Hz), 3.60(1H, dd, J=11.6Hz, 6.7Hz), 3.78(1H, dd, J=11.6Hz, 6.7Hz), 4.11-4.17(2H, m), 5.02 (2H, s), 6.85-6.94(3H, m), 7.12-7.17(2H, m), 7.22(1H, t, J=7.8Hz), 7.30-7.40(6H, m)

<Example 214>

Methyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxymethyloxymethyl-2-propargylpentanoate



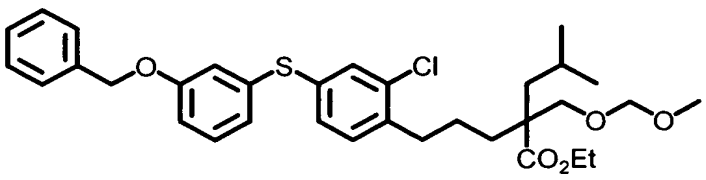
The compound of Example 212 (1.12g) was dissolved in acetonitrile (30mL). To this solution, diisopropylamine (0.58mL) and MOMCl (0.25mL) were added while the solution was stirred and chilled in an ice bath. The mixture was stirred overnight. Subsequently, water was added and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous magnesium sulfate. The solvent was concentrated and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 5:1) to give the desired product as a colorless oil (1.12g).

MS(EI): 552 $[M]^+$

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.45-1.50(1H, m), 1.59-1.73(3H, m), 1.94(1H, t, J=2.4Hz), 2.56-2.73(4H, m), 3.33(3H, s), 3.57-3.74(5H, m), 4.59(2H, s), 5.02 (2H, s), 6.85-6.94(3H, m), 7.10-7.16(2H, m), 7.22(1H, t, J=7.9Hz), 7.32-7.39(6H, m)

<Example 215>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-isobutyl-2-methoxymethyloxymethylpentanoate



Using the compound of Example 213, the reaction was carried out in the same manner as in Example 214 to give the

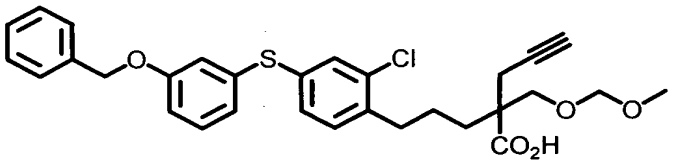
desired product as a yellow oil.

MS(EI): 584 $[M]^+$

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.83(3H, d, J=6.8Hz), 0.85(3H, d, J=6.8Hz), 1.24(3H, t, J=7.3Hz), 1.45-1.76(7H, m), 2.69(2H, t, J=7.3Hz), 3.32(3H, s), 3.57(1H, d, J=9.8Hz), 3.65(1H, d, J=9.8Hz), 4.08-4.14(2H, m), 4.57(2H, s), 5.02 (2H, s), 6.85-6.95(3H, m), 7.11-7.16(2H, m), 7.22(1H, t, J=7.8Hz), 7.30-7.41(6H, m)

<Example 216>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxymethyloxymethyl-2-propargylpentanoic acid



The compound of Example 214 (1.12g) was dissolved in a mixed solvent composed of MeOH: THF = 1:1 (12mL). To this solution, a 10% aqueous solution of sodium hydroxide (4mL) was added and the mixture was refluxed. After 20 hours, the mixture was diluted with water, and hydrochloric acid was added to make the mixture acidic. The mixture was then extracted with ethyl acetate and the extract was washed with a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous magnesium sulfate. The solvent was removed to give the desired product as a yellow

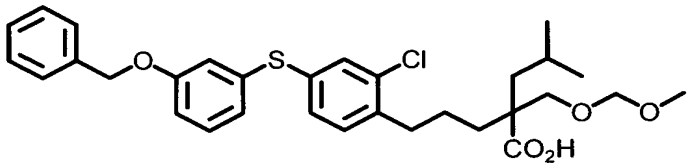
oil (1.09g).

MS(EI): 538 $[M]^+$

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.53-1.77(4H, m), 1.96(1H, t, J=2.4Hz), 2.59(1H, dd, J=17.1Hz, 2.4Hz), 2.68-2.73(3H, m), 3.33(3H, s), 3.69(1H, d, J=9.8Hz), 3.73(1H, d, J=9.8Hz), 4.60(2H, s), 5.01(2H, s), 6.85-6.93(3H, m), 7.11(1H, d, J=7.9Hz), 7.15(1H, dd, J=7.9Hz, 1.8Hz), 7.22(1H, t, J=7.9Hz), 7.30-7.40(6H, m)

<Example 217>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-isobutyl-2-methoxymethyloxymethylpentanoic acid



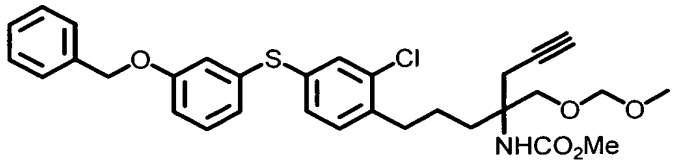
Using the compound of Example 215, the reaction was carried out in the same manner as in Example 216 to give the desired product as a yellow oil.

FABMS: 556 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.83(3H, d, J=6.8Hz), 0.85(3H, d, J=6.8Hz), 1.47-1.84(7H, m), 2.69(2H, t, J=7.3Hz), 3.31(3H, s), 3.56(1H, d, J=9.2Hz), 3.65(1H, d, J=9.2Hz), 4.58(2H, s), 5.01 (2H, s), 6.86(1H, dd, J=8.6Hz, 2.4Hz), 6.90-6.94(2H, m), 7.11-7.16(2H, m), 7.22(1H, t, J=7.8Hz), 7.30-7.40(6H, m)

<Example 218>

7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-methoxycarbonylamino-4-methoxymethyloxymethyl-1-heptin



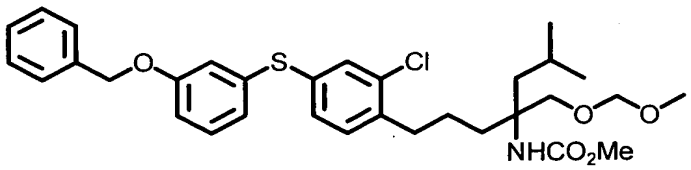
Using the compound of Example 216, the reaction was carried out in the same manner as in Example 163 to give the desired product as a colorless oil.

FABMS: 568 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.57-1.66(4H, m), 1.85-1.93(1H, m), 1.99(1H, t, J=2.4Hz), 2.00-2.05(1H, m), 2.64-2.75(4H, m), 3.35(3H, s), 3.61(3H, s), 3.62(1H, d, J=9.8Hz), 3.71(1H, d, J=9.8Hz), 4.61(2H, s), 4.92(1H, s), 5.01(2H, s), 6.85-6.94(3H, m), 7.12-7.17(2H, m), 7.22(1H, t, J=7.9Hz), 7.30-7.40(6H, m)

<Example 219>

7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-methoxycarbonylamino-4-methoxymethyloxymethyl-2-methylheptane



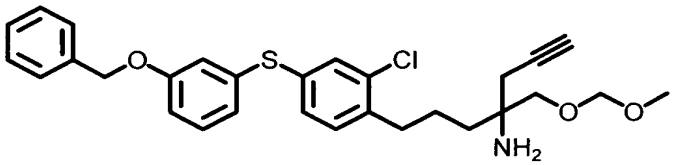
Using the compound of Example 217, the reaction was carried out in the same manner as in Example 163 to give the desired product as a yellow oil.

MS(EI): 585 $[M]^+$

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.91(3H, d, J=6.8Hz), 0.92(3H, d, J=6.8Hz), 1.58-1.82(7H, m), 2.68(2H, t, J=7.3Hz), 3.34(3H, s), 3.56(3H, s), 3.78(1H, d, J=11.0Hz), 3.87(1H, d, J=11.0Hz), 4.59(2H, s), 4.70(1H, s), 5.02(2H, s), 6.82-6.94(3H, m), 7.11-7.14(2H, m), 7.17-7.24(1H, m), 7.32-7.39(6H, m)

<Example 220>

4-amino-7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-methoxymethyloxymethyl-1-heptin



Using the compound of Example 218, the reaction was carried out in the same manner as in Example 184 to give the desired product as a colorless oil.

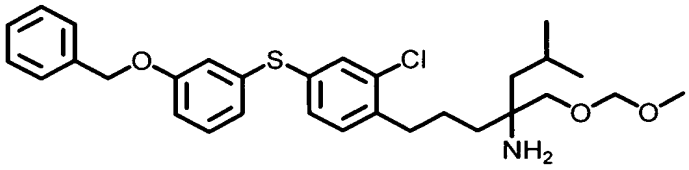
MS(EI): 509 $[M]^+$

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.51(2H, br), 1.56-1.68(4H, m), 2.01(1H, t, J=2.4Hz), 2.32(1H, dd, J=16.5Hz, 2.4Hz), 2.38(1H, dd, J=16.5Hz, 2.4Hz), 2.71(2H, t, J=7.3Hz), 3.35(3H, s), 3.37(1H, d, J=9.2Hz), 3.43(1H, d, J=9.2Hz), 4.62(2H, s), 5.02(2H, s), 6.87(1H, dd, J=8.6Hz, 2.4Hz), 6.91-6.94(2H, m), 7.15(2H, s), 7.22(1H, t, J=7.9Hz), 7.30-7.41(6H, m)

<Example 221>

4-amino-7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-

methoxymethyloxymethyl-2-methylheptane



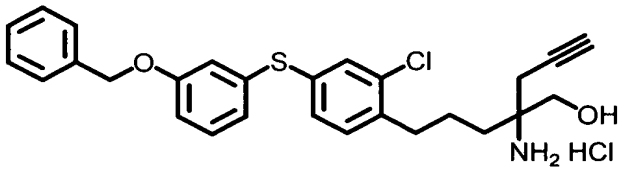
Using the compound of Example 219, the reaction was carried out in the same manner as in Example 184 to give the desired product as a colorless oil

MS(EI): 527 $[M]^+$

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.93(3H, d, J=6.8Hz), 0.94(3H, d, J=6.8Hz), 1.24-1.32(4H, m), 1.48-1.62(4H, m), 1.68-1.75(1H, m), 2.69(2H, t, J=7.3Hz), 3.27(1H, d, J=9.2Hz), 3.32(1H, d, J=9.2Hz), 3.35(3H, s), 4.61(2H, s), 5.01(2H, s), 6.86(1H, dd, J=7.9Hz, 2.4Hz), 6.91-6.94(2H, m), 7.12-7.17(2H, m), 7.22(1H, t, J=7.9Hz), 7.30-7.40(6H, m)

<Example 222>

2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-propargylpentane-1-ol hydrochloride



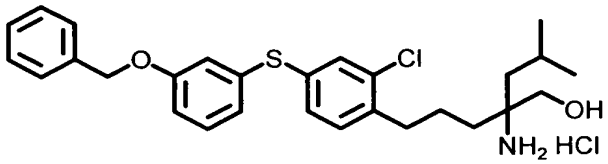
Using the compound of Example 220, the reaction was carried out in the same manner as in Example 76 to give the desired product as a colorless amorphous.

FABMS: 466 ($[M+H]^+$)

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.65(4H, br s), 2.67(2H, t, J=7.3Hz), 3.08(1H, s), 3.46(2H, br), 5.10(2H, s), 5.56(1H, br), 6.91(1H, d, J=7.9Hz), 6.96-7.02(2H, m), 7.24(1H, dd, J=7.9Hz, 1.8Hz), 7.30-7.40(8H, m), 7.88(3H, br)

<Example 223>

2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-isobutylpentane-1-ol hydrochloride



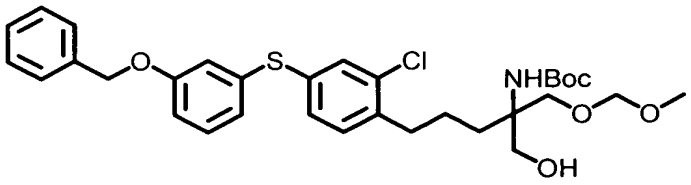
Using the compound of Example 221, the reaction was carried out in the same manner as in Example 76 to give the desired product as a colorless oil.

FABMS: 484 ([M+H]$^+$)

^{1}H-NMR(400MHz, DMSO-d_6) δ 0.84(3H, d, J=6.7Hz), 0.86(3H, d, J=6.7Hz), 1.07-1.18(2H, m), 1.29-1.33(2H, m), 1.48-1.55(2H, m), 1.62-1.68(1H, m), 2.62(2H, t, J=7.3Hz), 3.07(1H, d, J=9.8Hz), 3.11(1H, d, J=9.8Hz), 4.44(1H, br), 5.09(2H, s), 6.88-7.00(3H, m), 7.22(1H, dd, J=7.9Hz, J=1.8Hz), 7.29-7.42(8H, m)

<Example 224>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethyloxymethylpentane-1-ol



2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-2-t-butoxycarbonylamino-1,3-propanediol (5.00g) was dissolved in MeCN (100mL). While the solution was chilled in an ice bath, diisopropylethylamine (2.03mL) and MOMCl (0.88mL) were added. Subsequently, the mixture was stirred for 16 hours while being allowed to warm to room temperature. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed with a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous magnesium sulfate. The solvent was concentrated and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 2:1) to give the desired product as a colorless oil (2.36g).

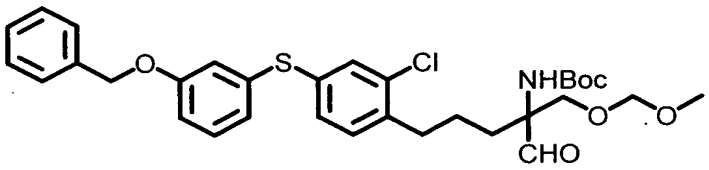
FABMS: 602 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.54-1.68(4H, m), 1.81-1.86(1H, m), 2.70(2H, t, J=7.3Hz), 3.34(3H, s), 3.46(1H, d, J=9.8Hz), 3.63-3.72(3H, m), 3.99(1H, br), 4.60(2H, s), 5.02(2H, s), 5.07(1H, br), 6.87(1H, dd, J=8.6Hz, 2.4Hz), 6.91-6.95(2H, m), 7.11-7.16(2H, m), 7.22(1H, t, J=7.9Hz), 7.30-7.43(6H, m)

<Example 225>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-

butoxycarbonylamino-2-methoxymethyloxymethylpentanal



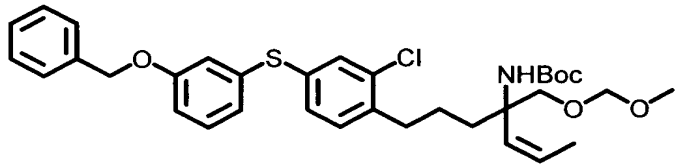
Using the compound of Example 224, the reaction was carried out in the same manner as in Example 133 to give the desired product as a colorless oil.

FABMS: 600 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.54-1.60(2H, m), 1.77-1.84(1H, m), 2.00-2.15(1H, m), 2.68(2H, t, J=7.3Hz), 3.30(3H, s), 3.78(1H, d, J=9.8Hz), 3.98(1H, d, J=9.8Hz), 4.57(2H, s), 5.02(2H, s), 5.39(1H, br), 6.86-6.95(3H, m), 7.07-7.14(2H, m), 7.21-7.39(7H, m), 9.40(1H, s)

<Example 226>

7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-t-butoxycarbonylamino-4-methoxymethyloxymethyl-3-heptene



$EtPh_3PI$ (906mg) was dissolved in THF (20mL). To this solution, LDA (2.20mL), chilled to -78°C, was added under atmosphere of argon gas and the mixture was stirred for 10min. Subsequently, the mixture was stirred at 0°C for 5min and was then chilled again to -78°C, followed by the dropwise addition

of a THF solution (10mL) of the compound of Example 225 (1.00g). The mixture was further stirred at -78°C for 1 hour and at room temperature for 1 hour. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed with a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous magnesium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 4:1) to give the desired product as a yellow oil (172mg).

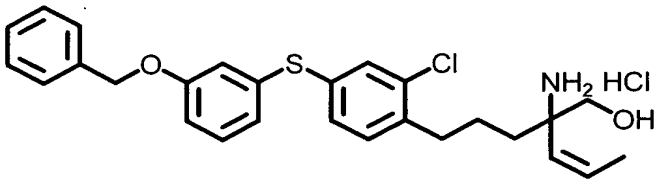
FABMS: 612 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.41(9H, s), 1.60-1.66(2H, m), 1.74(3H, dd, J=7.3Hz, 1.8Hz), 1.89-1.93(2H, m), 2.69(2H, t, J=8.0Hz), 3.34(3H, s), 3.64(1H, d, J=9.2Hz), 3.71(1H, d, J=9.2Hz), 4.60(2H, s), 4.83(1H, br), 5.02(2H, s), 5.30(1H, br d, J=12.2Hz), 5.54-5.57(1H, m), 6.86(1H, dd, J=8.0Hz, 2.4Hz), 6.91-6.94(2H, m), 7.11-7.16(2H, m), 7.22(1H, t, J=7.9Hz), 7.30-7.41(6H, m)

<Example 227>

3-amino-7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-4-hydroxymethyl-3-heptene hydrochloride

Using the compound of Example 226, the reaction was carried out in the same manner as in Example 76 to give the desired product as a colorless oil.



FABMS: 468 ($[M+H]^+$)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.61-1.75(4H, m), 1.77(3H, dd, J=7.3Hz, 1.8Hz), 2.70(2H, t, J=8.0Hz), 3.37(1H, d, J=10.4Hz), 3.46(1H, d, J=10.4Hz), 5.01(2H, s), 5.19(1H, d d, J=12.2Hz, 1.8Hz), 5.55(1H, dq, J=12.2Hz, 7.3Hz), 6.87(1H, dd, J=7.8Hz, 2.4Hz), 6.91-6.94(2H, m), 7.12-7.17(2H, m), 7.22(1H, t, J=7.9Hz), 7.31-7.40(6H, m)

<Exemplary Experiment>

Inhibitory effects of test compounds on host vs graft reaction in mice

This experiment was performed according to the method described in *Transplantation* 55(3) (1993): 578-591. Spleens were collected from 7 to 12 week old male BALB/c mice (available from CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). The spleens were placed in an RPMI-1640 medium (SIGMA, GIBCO INDUSTRIES Inc., or IWAKI GLASS Co., Ltd.) and were gently pressed between two slide glasses and then passed through a cell strainer (70μm, Falcon) to form a cell suspension. The suspension was then centrifuged and the supernatant was discarded. An ammonium chloride-Tris isotonic buffer was added to the suspension to lyse erythrocytes. The

cells were then centrifuged three times in RPMI-1640 medium for washing and were resuspended in an RPMI-1640 medium. To this suspension, mitomycin C (KYOWA HAKKO KOGYO Co., Ltd.) was added to a final concentration of 25μg/mL and the suspension was incubated for 30 minutes at 37°C in a 5% CO_2 atmosphere. The cells were centrifuged three times in RPMI-1640 medium for washing and were resuspended in an RPMI-1640 medium so that the medium would contain 2.5 X 10^8 cells/mL. This suspension served as a "stimulation cell suspension." Using a 27G needle, along with a microsyringe (Hamilton), 20μL (5 X 10^6 cells/mouse) of the stimulation cell suspension was subcutaneously injected into the right hind footpad of 6 to 12 week old male C3H/HeN mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). As a normal control group, a group of mice were injected with RPMI-1640 medium alone. 4 days after the injection, right popliteal lymph nodes were collected and were weighed on a Mettler AT201 electronic scale (METTLER TOLEDO Co., Ltd.). Each animal was intraperitoneally administered a test compound once a day for four consecutive days starting on the day of the injection of the stimulation cells (*i.e.*, total of 4 times). As a control group, a group of the animals were administered the same solvent as that used in the preparation of each test compound. The results are shown in Table 16 below:

Table 16

Example No.	Dose (mg/kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)
84	10	79	151	0.03	65
96	10	73	184	0.1	45
101	0.3	44	185	0.1	88
102	1	46	188	0.1	78
127	10	57	189	0.03	71
131	0.3	57	191	0.1	41
135	1	69	192	0.1	86
136	3	74	194	0.1	70
137	3	70	196	0.03	63
138	10	66	197	0.03	54
139	10	55	199	0.3	71
140	3	60	209	0.03	71
143	0.3	60	222	0.3	57
145	0.3	64	223	0.3	70
148	0.3	71	227	0.3	58

As has been demonstrated by the results, each of the compounds of the present invention represented by the general formula (1) has proven to be effective in the animal model.

INDUSTRIAL APPLICABILITY

As set forth, the present invention has been devised in recognition of the fact that the novel amino alcohol derivatives with a diarylsulfide or diarylether group exhibit strong immunosuppressive effects, the effects particularly significant when one of the aryl groups includes, at its para-position, a carbon chain with an amino alcohol group and the other aryl group includes a substituent at its meta-position. Effective immunosuppressors, the compounds of the present invention have a great potential as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation, autoimmune diseases, rheumatoid arthritis,

psoriasis, atopic dermatitis, bronchial asthma, pollinosis and various other diseases.